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BRITISH MEDICAL JOURNAL

LONDON SATURDAY JULY 18 1959

RAPIDLY ACTING THYROID HORMONES AND THEIR CARDIAC ACTION

BY

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Those two synthesized thyroid hormones triiodothyronine and triac (Pitt-Rivers, 1953) not only can provide full thyroid replacement therapy for myxoedema, but will do this more rapidly than the main thyroid hormone L-thyroxine (Asper *et al.*, 1953; Trotter, 1955). The discovery of the rapid action of triiodothyronine initially led to the suggestion that it may be the form in which the thyroid hormone acts in the tissues (Gross and Pitt-Rivers, 1952), but this hypothesis was abandoned when triiodothyronine was found to have no action on tissue slices *in vitro* (Thibault and Pitt-Rivers, 1955). The second analogue, triac, which is the acetic acid derivative of triiodothyronine, was found in its first clinical and biological trials to have at least as rapid an action (Trotter, 1955, 1957; Frazer *et al.*, 1956; Zondek *et al.*, 1956; Macgregor, 1957; Goolden, 1957) and to have also an immediate action on tissue slices *in vitro* (Thibault and Pitt-Rivers, 1955; Thibault, 1957), although this latter finding has not been confirmed (Barker and Lewis, 1956; Wiswell and Asper, 1958)

Other clinical studies have also claimed that small doses of triac can lower blood cholesterol without other equivalent thyroid effects (Lerman and Pitt-Rivers, 1955; Trotter, 1956, 1957). Thus triac might have special clinical uses, both when the rapid restoration of thyroid function is desired, as in cases of myxoedema coma, and also possibly for lowering blood cholesterol in, for example, patients with coronary atheroma. The following studies were therefore undertaken to assess how soon triac acted and whether it did specifically lower plasma cholesterol; the studies were made on myxoedematous subjects, and its action was contrasted with that of triiodothyronine, the more familiar rapidly acting thyroid hormone. In the first studies the metabolic effects of a single large oral dose of triac or triiodothyronine, given to myxoedematous subjects, were observed closely for the first 24 hours, and thereafter for several days. Where possible, the effects of both drugs were observed on each patient, the second dose being given after an adequate interval of 7 to 28 days. In the later studies the pattern of the restoration of thyroid function was observed after administration of various graded daily dosages of triac, noting also its cardiac effects and contrasting it with triiodothyronine.

Material and Methods

The large single dose of triac or triiodothyronine was given only to myxoedematous subjects who were judged unlikely to have coronary artery disease. These patients were therefore without any clinical or E.C.G. evidence of this disease, and were also under 40 years or had only had a short period of myxoedema, or had previously had full thyroid replacement therapy without disability. Of the six patients, all showed the signs of complete thyroid failure, and two had an associated hypopituitarism (Ibbertson and Fraser, 1956). The six patients observed for longer periods on various daily dosages of triac included two of the above patients and also four others with complete thyroid failure. Some incidental observations made on other patients given triac are also noted.

Dosage of Triac and Triiodothyronine

For the single-dose experiments, triac was given in oral doses of 18 and 12 mg., which is about three times the full daily replacement dose (occasional doses of 6 and 10 mg. being also used). Triiodothyronine was given in a single oral dose of 0.5 mg., which is about seven times the daily replacement dose. These doses were chosen to obtain a readily measurable effect, with the balance set in favour of triiodothyronine, since it was planned to ascertain whether there was any earlier action of triac not attributable merely to the size of the physiological dose of hormone given. For human myxoedematous subjects the daily full replacement dosage has been estimated as about 4–6 mg. of triac (Lerman and Pitt-Rivers, 1955; Trotter, 1956, 1957) and 0.07–0.1 mg. a day of triiodothyronine (Selenkow and Asper, 1955a). Doniach *et al.* (1958) found some metabolic effects from 0.08 mg. of triiodothyronine a day given to normals but little if any from 4 mg. of triac, suggesting that this is slightly more than the replacement dosage for triiodothyronine, but about that for triac.

Procedure for Studies after a Single Dose

With the scheme of sedation described below, comparable observations of six patients were made under basal conditions during 18 test days. With four patients three test days were observed—that of the placebo, of the triac, and of the triiodothyronine dose, usually in that order; with one patient (J. W.) the triiodothyronine day preceded the triac day. A further two patients received one or other of these drugs on a single test day. During each test day serial measurements of the B.M.R., E.C.G., plasma cholesterol, and urine volume, creatine, and creatinines were made on all patients; and also of urine phosphate on one patient. To permit comparison of the effect observed in the different patients, the metabolic effects measured are presented as a percentage of each patient's initial value for that test day.

Maintenance of Basal State During Test Days.—The study of the changes in the B.M.R. within a 24-hour period was made possible by an extended use of the sedated B.M.R. procedure. Thus on a "test day" the

patient was first sedated with sodium amylobarbitone 200 mg., given at 7 a.m. and 9 a.m. The test dose of the drug to be studied was given at 9 a.m. The patients were allowed to sleep throughout the day, being wakened to pass urine only after the two-hourly B.M.R. and E.C.G. estimations. A further dose of sodium amylobarbitone was given if signs of rousing were observed during the day. Sips of water were allowed throughout the day if desired. On the morning following each trial day the patients were similarly sedated, and after a B.M.R. recording were wakened for breakfast with oral doses of bemegride (Ibbertson *et al.*, 1957). By these means, reliable serial B.M.R. readings were obtained without inconvenience to the patient. The adequacy of the attainment of basal conditions was confirmed by the observations on four of the patients made throughout a control day under exactly the same conditions after giving placebo tablets instead of triac or triiodothyronine (see Fig. 1).

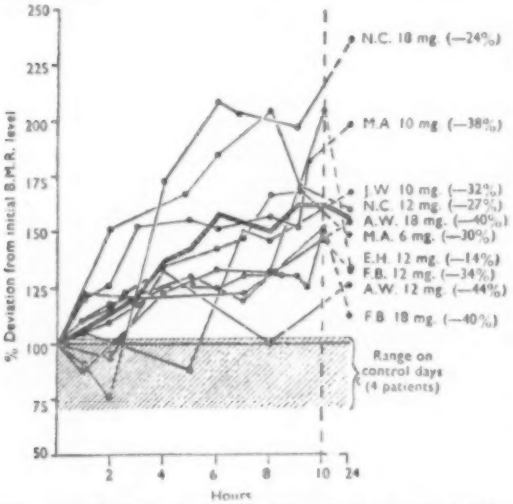
% Deviation from initial B.M.R. level
Hours
N.C. 18 mg. (—24%)
M.A. 10 mg. (—38%)
J.W. 10 mg. (—32%)
N.C. 12 mg. (—27%)
A.W. 18 mg. (—40%)
M.A. 6 mg. (—30%)
E.H. 12 mg. (—14%)
F.B. 12 mg. (—34%)
A.W. 12 mg. (—44%)
F.B. 18 mg. (—40%)
Range on control days (4 patients)

FIG. 1.—Early effect of 10 single doses of triac on the B.M.R. compared with the range observed on four control days (on myxoedematous subjects).

Measurements

Sleeping B.M.R. determinations were performed by the method described by Fraser and Nordin (1955), using Benedict–Roth apparatus and the standards of Robertson and Reid (1952). The results were first calculated as a percentage of the mean expected normal for age and sex.

E.C.G. recordings were made after each B.M.R. determination on both test days and control days. Although changes were observed in the potentials of both T and R waves, the latter were more easily measured and proved the more sensitive index of the minimal thyroid hormone effect. Standard lead 1 was usually measured, although lead 2 occasionally showed a more obvious change.

Serum cholesterol determinations were performed in duplicate by the method of Zlatkis *et al.* (1953), and urine phosphate and creatinine by the method of King and Wootton (1956).

Effects Within 24 Hours of a Single Dose

(a) B.M.R.

Serial measurements of the B.M.R. throughout a day are feasible only if the patient can be maintained in a basal state, which is not possible under normal resting conditions (Lerman and Pitt-Rivers, 1955). In these studies, as described under "Methods," heavy sedation throughout the test day ensured a basal state, and incidentally minimized the boredom of the procedure of a test day for the patient. The adequacy of the procedure in maintaining a basal state is shown in the results obtained with four patients on the control days when they were given placebo tablets (Fig. 1). Initial B.M.R. values ranged from −6 to −39%, and each patient's subsequent measurements were within a range of 71–108% of these initial B.M.R. values. Thus on control days there was some tendency for the B.M.R. to fall even lower as the day wore on; clearly, therefore, any rise observed during the test days after triac or triiodothyronine was likely to be due to the drug.

After the single large oral dose of triac (6–18 mg.) there was within the 24 hours a definite rise in the B.M.R. in all 10 test days on the six patients (Fig. 1). This rise was evident at least by the fourth hour, when the values were over 120% of the initial reading. The peak effect was achieved between the 6th and 24th hours, usually with a rise of at least 50% above the morning's initial value.

Since other workers have not observed so early a rise with triiodothyronine, it seemed important to determine whether a similar early effect could be achieved with rather more than the physiologically equivalent dose of triiodothyronine. Fig. 2 contrasts the results obtained

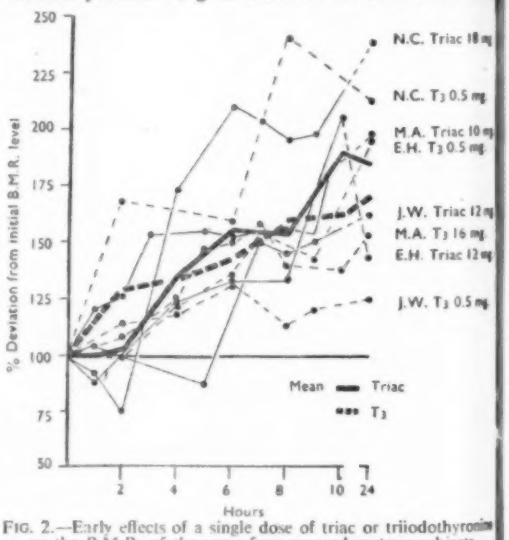

FIG. 2.—Early effects of a single dose of triac or triiodothyronine on the B.M.R. of the same four myxoedematous subjects.

after single oral doses of 0.5 mg. of triiodothyronine with those observed after doses of 10–18 mg. of triac in the same four persons. A very comparable rise in the B.M.R. is seen; the mean B.M.R. values during the first 24 hours after either drug are practically identical, though there is a hint that the peak may be achieved later at a slightly lower level after triiodothyronine.

(b) E.C.G.

During the first 24 hours after triac the E.C.G. voltage also rose in all patients. There was a rise by the fourth hour in four out of seven, and by the ninth hour in six out of seven patients. Full restoration of the E.C.G. to normal was not achieved with the single dose, but the R wave usually rose by 60–100%; the extent of this

response was not related to the size of the dose or to the initial R-wave voltabe. Fig. 3 compares these E.C.G changes after triac with those observed in the same patients on another day following use of triiodothyronine

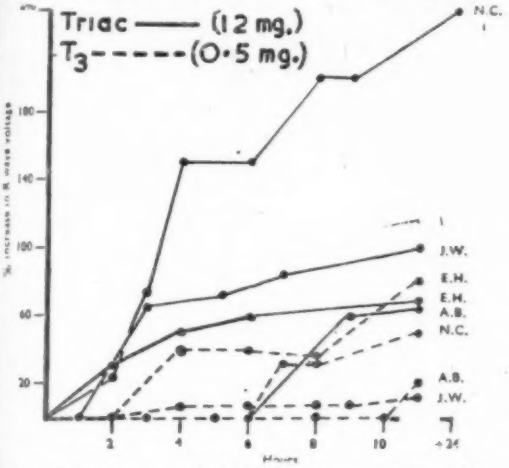

FIG. 3.—Early effect of a single dose of triac or triiodothyronine on hte E.C.G. of the same four myxoedematous subjects.

After triiodothyronine the rises in R-wave voltage were later and less marked than after triac ; only two E.C.G.s showed a change at four hours, and only three at nine hours

(c) Cholesterol (Fig. 4)

One patient (N. C.) is exceptional in showing a poorly sustained fall after either drug, possibly because previous thyroid hormone administration had been stopped only

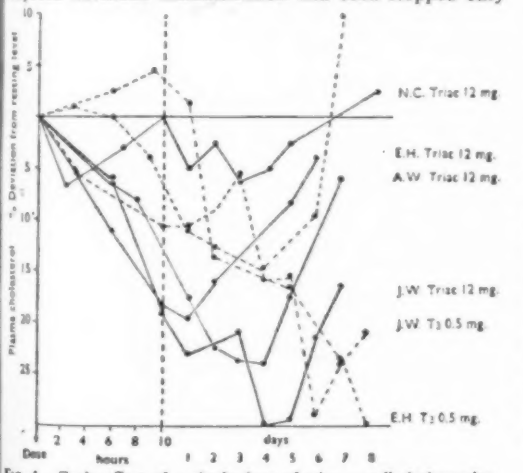

FIG. 4.—Early effect of a single dose of triac or triiodothyronine on the plasma cholesterol of four myxoedematous subjects.

45 days previously. Otherwise, after both triac and triiodothyronine a fall is discernible within the first 24 hours. After triac it is discernible at 6–18 hours, and at 24 hours it was approximately maximal at about 15% below the initial level. On the other hand, the fall after triiodothyronine was not clearly discernible before 24 hours, though it fell about as far as after triac.

(d) Urinary Creatine (Fig. 5)

After triac an increased creatine excretion was observed in six out of eight tests on three of four patients, beginning at the 8th to 12th hour and with a

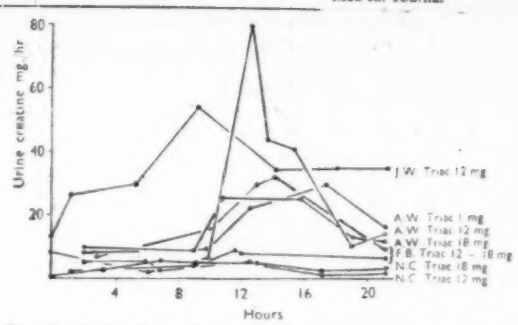

FIG. 5.—Early effect of a single dose of triac on the urinary creatine of four myxoedematous subjects.

peak at the 9th to 17th hour. No change was observed in urinary creatine after triiodothyronine with two of these patients, nor with three of them on control or placebo days

(e) Urinary Phosphate

In one patient a rise in urinary but not plasma phosphate was observed after both triac and triiodothyronine, with maximal levels between the 6th and 24th hours, and an earlier and greater effect was seen after triac, as also seen by Rall *et al.* (1956) on 24-hour samples.

(f) Varying Responsiveness Among the Patients

While both hormones produced responses in all the patients tested, the main variations seen in the speed and extent of action seemed to be a feature of the patient, more than of the dose or type of hormone. The patients whose E.C.G. or B.M.R. responded slowly to triac also responded slowly to triiodothyronine. Thus, patients A. W. and F. B., the two patients showing the slowest and weakest B.M.R. responses to triac, were similarly slow and weak in their E.C.G. response to it and also in both these responses to triiodothyronine. When one of these patients was given a smaller dose of triac (1 mg.), the responses were still slight. Both patients were previously untreated, one having primary myxoedema and the other hypopituitarism with complete thyroid failure. Slowness in response might have depended in part on the duration of previous hypothyroidism (Thibault, 1957), for the "early responders" were all patients who had previously been maintained on thyroid hormone, and in one instance it had been withdrawn only 45 days before the tests. As already noted, after either drug responses were seen in all the parameters observed ; excepting only the creatine response, which failed in one of four patients after triac and in both patients tested after triiodothyronine. A larger dose would probably be needed for the regular production of this effect.

Persistence of Effects of a Single Oral Dose of 12–18 mg. of Triac (Fig. 6)

As noted above, the peak effect was achieved within 24 hours ; after which the effects on the B.M.R., E.C.G., and cholesterol slowly subsided, reaching the basal level within 6 to 10 days, at approximately equivalent speeds. The rise in urinary creatine, however, lasted only until the third day. One patient's cholesterol level seemed exceptional in remaining low for longer. It is of interest to contrast this declining effect from 24 hours after the single dose with the steadily rising effect over the first week, seen when the maintenance dose is given daily (Fig. 7).

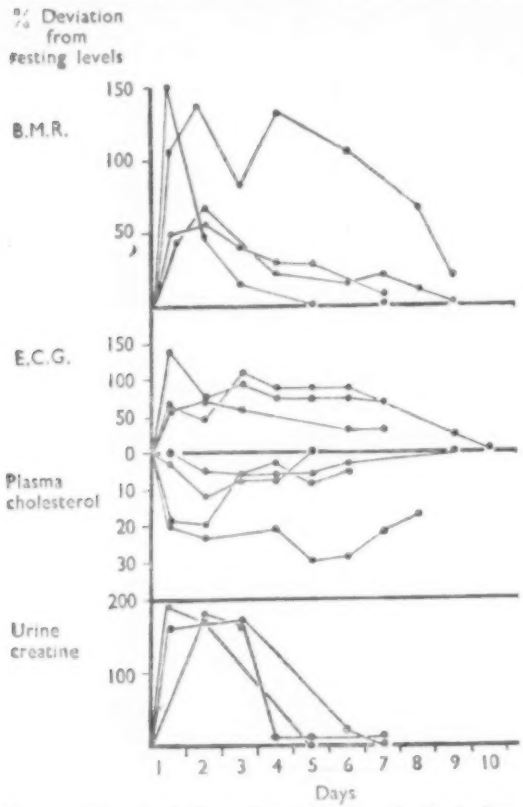

FIG. 6.—Duration of effects of a single dose of triac in four myxoedematous subjects. (Dose range, 12–18 mg.)

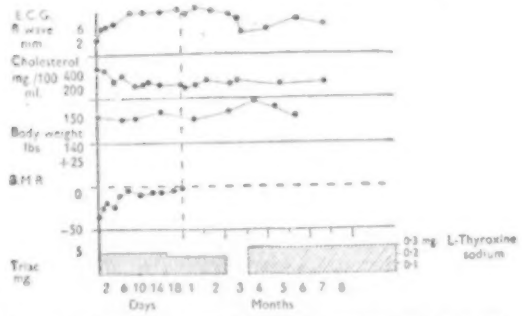

FIG. 7.—Effect on a myxoedematous subject of daily triac administration begun at maintenance dosage.

Effects of Daily Administration of Triac

Five patients with myxoedema were treated with triac for periods of 3 to 10 months before transferring them to thyroxine maintenance. Dosages ranged from 0.5 to 6 mg. a day. In two patients full maintenance dosage (4–6 mg. a day) was used from the start, and in three patients the treatment was begun with small doses and gradually increased to full maintenance dosage.

(1) When 5 mg. of triac a day was given from the start, a gradual restoration to normal was attained over 7 to 10 days (Fig. 7). The plasma cholesterol, E.C.G., and B.M.R. all showed the same rate of change.

(2) During the phase of lower initial triac dosage (0.5-1 mg. a day) all three patients showed a fall of plasma cholesterol, and in two this occurred without change in the B.M.R. or E.C.G. (Fig. 8). This pattern of change

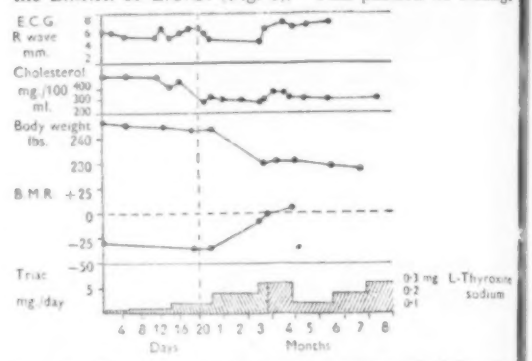

FIG. 8.—Effect on a myxoedematous subject of daily triac administration begun at small dosage.

corresponds to the apparently predominant cholesterol effect observed with triac by other workers. The third patient showed responses by all criteria even at the 1-2 mg. dose level, suggesting a heightened sensitivity to the drug. In all three patients the B.M.R. rose rapidly to normal levels after the increase of the dose to 4 mg. a day.

(3) For comparison, triiodothyronine was given similarly to two other myxoedematous subjects. During the early period of low dosage a similar phase of lowered cholesterol without discernible B.M.R. or E.C.G. change was also seen (Fig. 9).

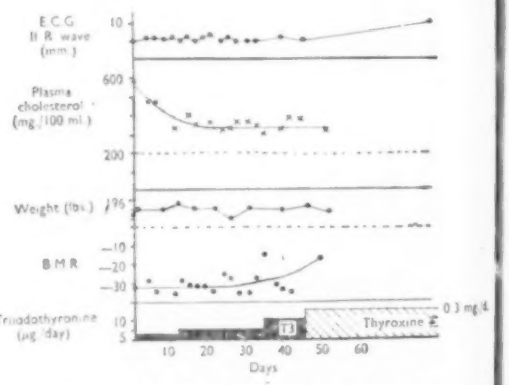

FIG. 9.—As in Fig. 8, but using triiodothyronine.

(4) *Frequency of dosage* (Fig. 10). The B.M.R. was twice studied throughout the day, on each of three patients, while they were being maintained on a constant total daily dose of triac (4, 4, and 2 mg. respectively). Throughout each day the patient was kept sedated and so basal, but the day's triac dose was subdivided on one day into 12-hourly and on the other into three-hourly doses. On both of the study days the patients were wakened to pass urine and drink water with each B.M.R. estimation, so that the regimes were comparably basal. On the 12-hourly triac regime (6 a.m. and 6 p.m.) the B.M.R.s were lowest in the morning, and all tended to be lower than those of the three-hourly regime. Thus each triac dose still shows some acute B.M.R. effect like that observed after the single large

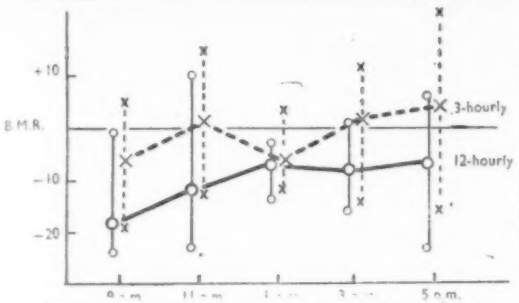

FIG. 10.—B.M.R. under the same daily dose of triac given three-hourly or 12-hourly (mean and ranges of the same three patients).

doses—that is, one beginning at about four hours and maximal at about eight hours. Consequently, a slight B.M.R. response from doses given only in the morning might not be discerned by the usual morning B.M.R. procedure.

Cardiac Effects of Small Doses of Triac

Myxoedematous subjects with known or suspected coronary ischaemia were given triac in small doses. Since triac has been suggested for patients with coronary disease (*Lancet*, 1956), thyroid function was cautiously restored with it in a series of 14 myxoedematous patients—in three a previous history of angina was elicited, in four there was no such history but an E.C.G. suggestive of coronary ischaemia, and in seven there were no such suggestions.

With the last group, satisfactory restoration of normal thyroid function was obtained without ischaemic episodes, using doses initially ranging from 0.25 to 0.5 mg., which were gradually increased to a maintenance dose of 4–6 mg. a day. The E.C.G. and plasma cholesterol were restored to normal within an average period of 10 days, though early changes were observed within 48 hours in all patients. The four patients with merely suggestions of coronary ischaemia on the E.C.G. were rendered euthyroid similarly—that is, by triac in commencing doses of 0.25 mg., increasing to a maximum of 4 mg. a day. No ischaemic symptoms were observed. In one patient the E.C.G. showed the normal evolutionary changes described without increase in ischaemia. In the other three, although the cholesterol fall followed the usual pattern, the E.C.G. showed little change in voltage and certainly no increase of ischaemia. It appears that ischaemic myocardial damage may in some way impair the ability of the E.C.G. to reflect changes in myocardial metabolism.

However, all three patients with a previous history of angina suffered ischaemic symptoms when triac therapy was begun (details are given in the Appendix)—in one previously untreated patient within 1½ hours after the first dose. The rapidity with which angina may be precipitated by even a small dose offers further evidence that these doses are not merely cholesterol-lowering in their action, as has previously been suggested from crude B.M.R. measurements. Barker (1955, 1957) has observed a similarly early cardiac effect from triac in thyroidectomized animals.

Clinical Uses of Triac

Diagnostic.—The rapid acute effects of triac on the E.C.G. may be of value in confirming the diagnosis of hypothyroidism in young subjects. For example, in a 5-months-old cretin, at eight hours after 0.5 mg. of triac by mouth, there was an obvious increase in the R and T waves of the E.C.G. The diagnosis of hypothyroidism was not obvious on clinical examination, but was later confirmed by radioiodine.

Therapeutic.—Where, as in this child, there is no reason to suspect coronary ischaemia, our studies have indicated that considerable restoration of thyroid function may be safely achieved within 24 hours by using triac or triiodothyronine. Optimal dosage should probably be a loading dose of 12–18 mg. of triac followed by 4–6 mg. a day in three divided doses. But where there is any history suggesting angina these rapidly acting thyroid hormones should be avoided. Where the subjects are over 40 years of age or there are E.C.G. or other suggestions of cardiac abnormality, the commencing dosage of triac should not exceed 0.25 mg. a day, which may be cautiously increased towards a full maintenance dosage over 10 or more days.

Discussion

It is clear from these studies that single doses of either triac or triiodothyronine produce discernible effects beginning at about four hours and maximal at about 8 to 12 hours, which involve evidently all parameters of thyroid function. Other workers in the clinical field have also testified to the rapid effect of these hormones. After each of these, Rall *et al.* (1956) and Wiswell and Asper (1958) have observed within 24 hours, and maximally within at least 48 hours, increased urinary volume, Na, Cl, N, P, creatine, and perhaps also calcium, and usually a rise in B.M.R. Occasionally effects have been observed before 24 hours: warming of the skin at four hours by Wiswell and Asper (1958) and a possible rise in B.M.R. at eight hours by Rawson *et al.* (1953). The sedation procedure which we have used has permitted the detection of these early B.M.R. changes well before 24 hours, which has not hitherto been practicable. The E.C.G. has also proved a convenient method of demonstrating these early thyroid effects.

These early B.M.R. and other changes contrasted with those observed after single doses of thyroxine, when they have not been discerned for several days or been maximal till about the tenth day (Asper *et al.*, 1953; Rawson *et al.*, 1953; Lerman and Pitt-Rivers, 1955; Fraser, 1958). Kyle *et al.* (1958) claim to have observed similarly rapid effects after 2 or 3 mg. of thyroxine, but their two patients had previously received a dose of triiodothyronine within 14 days, which would have altered their responsiveness. They also report observing an effect within two days after single 1,500-mg. doses of thyroid extract, but this rapidity may have been due to its content of triiodothyronine.

In speed of action there is little difference between triac and triiodothyronine, though our results suggest a slightly more rapid action from triac. While this observed difference might have depended merely on the dose of triac being physiologically greater, this is unlikely since this dose was about three to four times the daily maintenance dose while the triiodothyronine dose was about seven times. However, it is difficult to assess the physiologically equivalent single doses from the daily maintenance doses, as the persistence of their effects is different. We have observed the effects of triac persisting for only 7 to 10 days after the single dose, while Blackburn *et al.* (1954) have observed that the decline

of the effects from triiodothyronine has a half-life of 7.4 days and from thyroxine one of 11.9 days. The less persistent action of triac does suggest that its action may also be more rapid in onset.

It is of some theoretical interest that after a single dose of triac there is a maximal effect within 24 hours which gradually declines over the subsequent week, while the daily administration of a maintenance dosage of triac causes a steadily rising effect throughout the first week. This suggests that the full effects of the chronic administration of thyroid hormones are achieved in part by some responsive increase in tissue enzymes, such as that demonstrated by Smith and Williams-Ashman (1951). Our observtaions that the level of the B.M.R. throughout the day depends on the frequency of administration of the maintenance dosage of triac suggest that each dose still has an acute metabolic effect, while also maintaining some such increased enzyme responsiveness.

Our results do not reveal any qualitative difference between the effects of triac and those of triiodothyronine, the other thyroid hormone tested, contrary to certain previous claims (Lerman and Pitt-Rivers, 1955; Trotter, 1955, 1957; *Lancet*, 1956; Oliver and Boyd, 1957). While we have confirmed that small doses of triac may lower the cholesterol without any apparent effects on the morning B.M.R. or E.C.G., this has also been seen with small doses of triiodothyronine, and might possibly also be seen with equivalent doses of thyroxine (Strisower *et al.*, 1957). Further, small metabolic effects are difficult to measure, and frequent sedated B.M.R. estimations taken throughout the day have indicated that the usual morning B.M.R. may not reveal the maximal afternoon response which follows triac given only in the morning. In any case, cardiac stimulation has been observed within 1½ hours of giving these same small doses of triac to certain myxoedematous subjects.

Our observations have confirmed those of others (Mackay *et al.*, 1957; Oliver and Boyd, 1957) that even small doses (1/16 of the daily maintenance dose) of triac may precipitate angina in myxoedematous subjects with a history of angina. Hence any cautious restoration of thyroid function in such subjects should be done instead with the slower-acting thyroid hormones such as thyroxine (Wolff and Goldberg, 1957).

There are, however, two indications for the clinical use of these rapidly acting thyroid hormones: either for the cautious restoration of thyroid function over several days with E.C.G. control in cases of myxoedema coma, or for the recognition of suspected hypothyroidism in young subjects. In young subjects without any suspicion of cardiac disease, triac can correct the familiar hypothyroid abnormalities on the E.C.G. within eight hours, and so offers a useful quick therapeutic test. In older subjects such a test may be neither safe nor valid, for in myxoedematous subjects with coronary disease triac may not correct the E.C.G. abnormalities, and may precipitate angina.

APPENDIX

Acute Precipitation of Coronary Ischaemia by Triac

The three patients with a previous history of angina all suffered ischaemic symptoms when triac therapy was begun.

Case 1.—A 53-year-old woman, with myxoedema and hypoparathyroidism complicating thyroidectomy five years previously, suffered from angina on moderate effort. Examination revealed the presence of rheumatic heart disease with aortic stenosis and incompetence, and the E.C.G. showed a left bundle-branch block pattern. As she also suffered severe intractable (post-operative) tetany resistant to normal therapy, the restoration of thyroid function was thought desirable. Triac was begun in a dose of 0.25 mg. and gradually increased to 2 mg. a day. At this level she suffered a paroxysmal attack of precardial pain with collapse. Despite the L.B.B.B. pattern, the E.C.G. showed changes suggesting myocardial infarction. When the triac was stopped and anticoagulants were given, she recovered from this episode. This patient died five months later while on thyroid siccum, ¼ gr. (16 mg.) daily), and the post-mortem examination showed severe aortic stenosis, but no evidence of myocardial infarction.

Case 2.—A woman of 75 had been admitted to the surgical wards with large-bowel obstruction due to faecal impaction. She gave a history of sudden precardial pain some two to three months previously. Her myxoedema was obvious and the E.C.G. showed evidence of old posterior myocardial infarction. Treatment was begun with 0.5 mg. of triac daily. At 1½ hours after the first dose, she collapsed with palpitations and Cheyne-Stokes respiration. The E.C.G. showed sinus tachycardia with numerous extrasystoles, but no evidence of recent infarction. The patient was subsequently maintained on L-thyroxine, but died three weeks after the initiation of treatment. Post-mortem examination revealed extensive old and recent myocardial infarction.

Case 3.—A housewife already under treatment was first given triac at the age of 61. She had then suffered from angina on easy effort for five years, and had been diagnosed and treated as having myxoedema, after obtaining radio-iodine, cholesterol, and clinical evidence. Thus before giving triac, it had been ascertained that more than 0.05 to 0.1 mg. of L-thyroxine per day increased her liability to angina on effort, and so she was maintained on 0.05 mg. L-thyroxine per day. Then the thyroxine was stopped, and on three different days she was given single doses of triac of 1 mg., 0.75 mg., and 0.75 mg. On the first occasion, 2½ hours later she was giddy for one hour, on the second occasion, two hours later she had an angina attack for one hour; and on the third, three hours later she had an angina attack for five minutes. Subsequently she was stabilized on 0.25 mg. triac q.i.d., on which her clinical state was similar to that while receiving 0.05 to 0.01 mg. of thyroxine per day—that is, partial relief of her myxoedema, and probably less angina than without the thyroid hormone.

Summary

After single oral doses of 12–18 mg. of triac and of 0.5 mg. of triiodothyronine, effects were observed in myxoedematous subjects at as early as four hours and were maximal within 24 hours. These doses caused rises in sedated B.M.R., in the R wave of the E.C.G., in urinary creatine and phosphate, and a fall in plasma cholesterol.

Triac acted slightly more rapidly than triiodothyronine, and its effects lasted 7 to 10 days.

The daily administration of triac in maintenance doses to myxoedematous subjects, however, only gradually achieved a full effect within seven days. In smaller doses triac or triiodothyronine could induce a fall in plasma cholesterol without apparent B.M.R. or E.C.G. effect.

However, on constant daily dosage, triac given 12-hourly showed a lower B.M.R. in the morning than in the evening, or when given in three-hourly doses.

Even small doses of triac could rapidly induce angina in myxoedematous subjects who had given a history of

angina ; but triac may be the best thyroid hormone for treating subjects with myxoedema coma who do not give a history of angina

An E.C.G. may be taken eight hours after a dose of trial to confirm the diagnosis of hypothyroidism in young subjects

We have pleasure in acknowledging the considerable help of the sister and staff of the metabolic ward. Our thanks are due also to our colleagues who referred patients; to Miss M. Matthew, who performed some of the cholesterol determinations; and to the hospital technicians who made many of the B.M.R. and E.C.G. recordings. Dr. T. B. Binns, of Glaxo Laboratories Ltd., provided generous supplies of triac.

REFERENCES

Asper, S. P., jun., Selenkow, H. A., and Plamondon, C. A. (1953). *Bull. Johns Hopk. Hosp.*, **93**, 164.

Barker, S. B. (1955). *Ann. Rev. Physiol.*, **17**, 417

— (1957). *Ciba Foundation Colloquia on Endocrinology*, edited by G. E. W. Wolstenholme and E. C. P. Millar, **10**, 246. Churchill, London.

— and Lewis, W. J. (1956). *Proc. Soc. exp. Biol. (N.Y.)*, **91**, 650.

Blackburn, C. M., McConahey, W. M., Keating, F. R., jun., and Albert, A. (1954). *J. clin. Invest.*, **33**, 819.

Doniach, D., Hudson, R. V., Trotter, W. R., and Waddams, A. (1958). *Clin. Sci.*, **17**, 519.

Fraser, R. (1958). Unpublished observations

— Garrod, O., and Ibbertson, H. K. (1956). *J. Endocr.*, **14**, iii

— Hobson, Q. J. G., Arnott, D., and Emery, E. W. (1953). *Quart. J. Med.*, **22**, 99.

— and Nordin, B. E. C. (1955). *Lancet*, **1**, 532.

Goolden, A. W. G. (1957). *Ciba Foundation Colloquia on Endocrinology*, edited by G. E. W. Wolstenholme and E. C. P. Millar, **10**, 280. Churchill, London

Gross, J., and Pitt-Rivers, R. (1952). *Lancet*, **1**, 593.

Ibbertson, H. K., and Fraser, R. (1956). *Proc. roy. Soc. Med.*, **49**, 831.

— Joplin, G. F., and Fraser, R. (1957). *Brit. med. J.*, **1**, 928.

King, E. J., and Wootton, I. D. P. (1956). *Micro-analysis in Medical Biochemistry*, 3rd ed. Churchill, London.

Kyle, L. H., Canary, J. J., Meyer, R. J., and Pae, F. P. (1958). *J. clin. Endocr.*, **18**, 950.

Lancet, 1956, **1**, 896.

Lerman, J., and Pitt-Rivers, R. (1955). *J. clin. Endocr.*, **15**, 653.

Mackay, I. R., Goble, A. J., and Sparkes, F. (1957). *Med. J. Aust.*, **1**, 571.

Macgregor, A. G. (1957). *Ciba Foundation Colloquia on Endocrinology*, edited by G. E. W. Wolstenholme and E. C. P. Millar, **10**, 283. Churchill, London.

Oliver, M. F., and Boyd, G. S. (1957). *Lancet*, **1**, 124

Pitt-Rivers, R. (1953). Ibid., **2**, 234.

Rall, J. E., Pearson, O. H., Lipsett, M. B., and Rawson, R. W. (1956). *J. clin. Endocr.*, **16**, 1299

Rawson, R. W., Rall, J. E., Pearson, O. H., Robbins, J., Poppell, H. F., and West, C. D. (1953). *Amer. J. med. Sci.*, **226**, 405.

Robertson, J. D., and Reid, D. D. (1952). *Lancet*, **1**, 940.

Roche, J., Michel, R., and Jouan, P. (1956). *C.R. Soc. Biol. (Paris)*, **150**, 629.

Selenkow, H. A., and Asper, S. P., jun. (1955a). *J. clin. Endocr.*, **15**, 285.

— — (1955b). *Physiol. Rev.*, **35**, 426.

Smith, R. H., and Williams-Ashman, H. G. (1951). *Biochim. biophys. Acta*, **7**, 295.

Strisower, B., Gofman, J. W., Galioni, E. F., Rubinger, J. H., Pouteau, J., and Guzvich, P. (1957). *Lancet*, **1**, 120.

Thibault, O. (1957). *Ciba Foundation Colloquia on Endocrinology*, edited by G. E. W. Wolstenholme and E. C. P. Millar, **10**, 230. Churchill, London.

— and Pitt-Rivers, R. (1955). *Lancet*, **1**, 285.

Trotter, W. R. (1955). *Lancet*, **2**, 374.

— (1956). Ibid., **1**, 885

— (1957). *Ciba Foundation Colloquia on Endocrinology*, edited by G. E. W. Wolstenholme and E. C. P. Millar, **10**, 270. Churchill, London.

Wiswell, J. G., and Asper, S. P., jun. (1958). *Bull. Johns Hopk. Hosp.*, **102**, 115.

Wolff, J., and Goldberg, R. C. (1957). In R. H. S. Thompson and E. J. King's *Biochemical Disorders in Human Disease*, p. 318. Churchill, London.

Zlatkis, A., Zak, B., and Boyle, A. J. (1953). *J. Lab. clin. Med.*, **41**, 486.

Zondek, H., Leszynsky, H. E., and Zondek, G. W. (1956). *Lancet*, **2**, 255

MASSIVE JEJUNAL DIVERTICULOSIS WITH STEATORRHOEA AND MEGALOBLASTIC ANAEMIA IMPROVED BY EXCISION OF DIVERTICULA

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Diverticulosis of the small intestine, located largely in the jejunum, is a not uncommon pathological finding in elderly subjects, generally causing no symptoms and incidentally, found radiologically or at necropsy. Rarely diverticula are found to induce physical disorders. Taylor (1930) described the case of a patient with pernicious anaemia and a gastro-enterostomy in which numerous diverticula of the jejunum were found at necropsy. Montuschi (1949), Zingg (1950), Spang (1954), and Krevans, Conley, and Sachs (1954) described further cases in which jejunal diverticulosis had induced a sprue-like syndrome with diarrhoea, fatty stools, and hypoproteinaemia. The triad of jejunal diverticulosis, steatorrhoea, and megaloblastic anaemia was first recognized by Bauenoch and Bedford (1954) and by Dick (1955). A review of the literature reveals that only 21 cases have as yet been described, and 17 of them showed an associated megaloblastic anaemia. It is not yet firmly established that jejunal diverticulosis may itself be the cause of an associated malabsorption syndrome, which might be a chance association with the not uncommon lesion of the small intestine.

In this paper we are reporting a further case, not only because of the rarity of the condition, but also because elective surgical removal of the diverticula has brought a prolonged improvement in the patient's condition, with correction of both anaemia and steatorrhoea.

Case Report

A man aged 64, a finisher in a dye-works, was first seen at the Leeds General Infirmary in December, 1956. For 25 years he had had attacks of upper abdominal pain occurring about twice weekly. The pain was severe and colicky, persisting a few hours, and was accompanied by nausea and vomiting; his longest remission from pain was three months. In August, 1951, a particularly severe attack of pain with vomiting and diarrhoea necessitated admission to hospital. Blood examination revealed a haemoglobin of 60% (8.9 g./100 ml.) and a red-cell count of 3,400,000. Rapid improvement followed treatment with phthalylsulphathiazole and a blood transfusion. A diagnosis of acute gastroenteritis was made. Later a barium-meal study in November, 1951, revealed multiple diverticula of the upper jejunum to be present with prolonged retention of the bowel contents in them (Fig. 1).

In December, 1953, ligation and excision of third-degree haemorrhoids was performed, and after this operation the mild diarrhoea from which the patient had suffered since

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FIG. 1.—Barium-meal x-ray film in 1951.

1949 became persistent and severe. The bowels were opened five to six times every 24 hours, after every meal and two to three times during the night. The stools were fluid, foul, light-coloured, but not bulky, and were unaccompanied by blood and mucus. During this time increasing pallor, weakness, dyspnoea, and oedema of the legs were first noticed. Two years later (October, 1955) he collapsed while working and was not able to work thereafter, while in December exertional angina and repeated syncopal attacks developed. A weight loss of 42 lb. (19 kg.) occurred in the twelve months to December, 1956; no glossitis, dyspepsia, paraesthesiae, or ataxia had been observed.

On examination (December, 1956) nutrition was poor (weight, 116 lb—52.6 kg.), and there was marked pallor of skin and mucous membranes, with gross pitting oedema of the legs up to the knees. The tongue was clean and smooth but not reddened. There were no positive physical or abnormal neurological signs. The urine was free from albumin and sugar. Urgent admission to St. James's Hospital, Leeds, was arranged on December 8.

Blood examination revealed a severe macrocytic anaemia. The haemoglobin was 44% (6.51 g./100 ml.), red-cell count 2,600,000, and colour index 1.2. The M.C.V. and M.C.H.C. were both increased at 143 cubic microns and 32.5% respectively. Macrocytosis, anisocytosis, and poikilocytosis were present on the stained film. The platelets appeared to be reduced in number, and a mild leucopenia with a relative lymphocytosis was present—total white count 3,000 (polymorphs 40%, lymphocytes 60%). A sternal marrow examination on December 14 showed marked megaloblastic erythropoiesis. These findings, in conjunction with histamine-fast achlorhydria with a greatly reduced serum cyanocobalmin level (20 $\mu\mu$g./ml.*), suggested that either pernicious anaemia or a megaloblastic anaemia due to malabsorption complicating jejunal diverticulosis was present. Liver-function tests were normal except for a severe hypoproteinaemia—total proteins 4.3 g. (albumin 2.5 g., globulin 1.8 g.). The macroscopic appearances of the stools strongly suggested steatorrhoea, and this was confirmed biochemically later. There was no evidence of osteomalacia initially either radiologically or biochemically (calcium 9.1 mg./100 ml., phosphorous 3.5 mg./100 ml., serum alkaline phosphatase 9.7 units). Subsequently the serum calcium fell to 8.2–8.8 mg./100 ml., and the alkaline phosphatase rose to values between 22 and 30 units.

*Cyanocobalamin was assayed by the method of Hutner, Bach, and Ross (1956). In our hands the normal range is from 180 to 700 $\mu\mu$g./ml. Cases with pernicious anaemia usually fall in the low range below 110 $\mu\mu$g./ml. (Dossett and Droller, 1959).

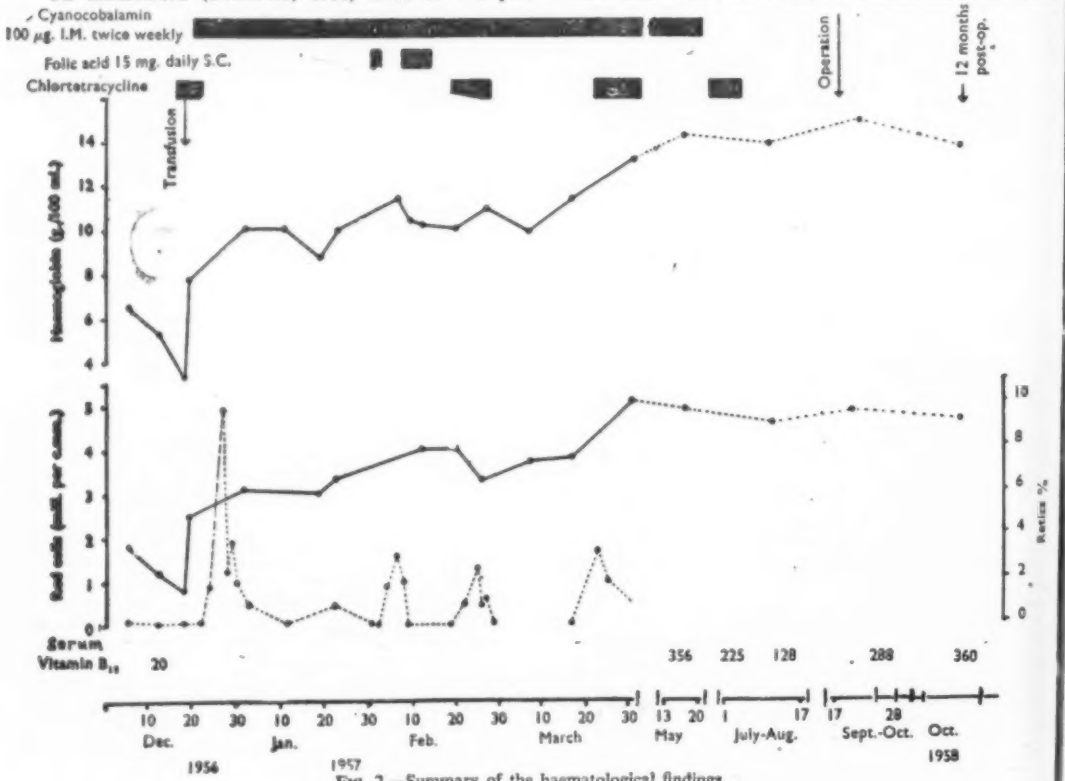

FIG. 2.—Summary of the haematological findings.

Progress and Treatment

By December 18 the patient's anaemia and general condition were much worse, his haemoglobin having fallen to 22% (3.3 g./100 ml.) and the red-cell count to 1,100,000 (Fig. 2). A transfusion effected a temporary improvement, but as there was a possibility that he might have pernicious anaemia, complicated incidentally by jejunal diverticulosis, treatment with cyanocobalamin injections had to be started on December 20, in a dose of 100 μg. twice weekly. At the same time a course of chlortetracycline, 1 g. daily, was given for five days because of intercurrent chest infection. A reticulocyte response of 9.8% on the seventh day followed this therapy, and by the 11th day the haemoglobin concentration had risen to 71% (10.5 g./100 ml.) and the red-cell count to 3,100,000. This response was suboptimal as judged by the severity of his anaemia. Continued cyanocobalamin therapy for the next month failed to raise the haemoglobin above 71% (10.52 g./100 ml.) or the red-cell count above 3,000,000.

The possibility of folic acid deficiency was considered and folic acid absorption and utilization studies were performed (Girdwood, 1953). These showed neither tissue depletion nor defective absorption to be present. However, as a minimal reticulocyte response (3.2%) had followed the oral and subcutaneous administration of 5 mg. of folic acid given for the test, more intensive therapy seemed desirable. Accordingly 15 mg. was injected daily for 10 days by subcutaneous injection, without improvement. Courses of chlortetracycline, given on two occasions, in each instance coincided with a slight reticulocyte response and produced improvement in the haematological picture (Fig. 2).

Further attempts at differential diagnosis were now made. Gastric juice removed after bethanecol chloride and alcohol stimulation contained neither acid nor pepsin, and uropepsin could not be detected in the urine. Gastroscopy (G. W.) showed a normal mucosa with a few areas of patchy gastric atrophy, far less than is usually present in pernicious anaemia, and a normal rugal pattern. Simultaneous gastric biopsy specimens obtained from the body and fundus of the stomach showed no mucosal atrophy. Gastric pits with well-formed mucous neck cells, few zymogenic cells, but no oxyntic cells were seen. The pathologist's opinion on these sections was that owing to the variability of the gastric histology in pernicious anaemia they could not be used to support or refute a diagnosis of pernicious anaemia. This view has been supported by the findings of Magnus (1958).

Throughout his stay in hospital, diarrhoea with bulky stools persisted, and steatorrhoea was demonstrated biochemically on several occasions. Hypoproteinaemia, which was present initially, showed a gradual improvement under treatment, total protein levels rising from 3.6 g. in December, 1956, to 5.1 g. in March, 1957. Plasma albumin levels rose from 2.2 to 3.2 g. over the same period.

After chlortetracycline therapy the stools would become formed and less numerous for a few days, but would relapse again towards the end of the week's course. The patient was discharged on March 28, his anaemia corrected, hypoproteinaemia improved, but diarrhoea persisting.

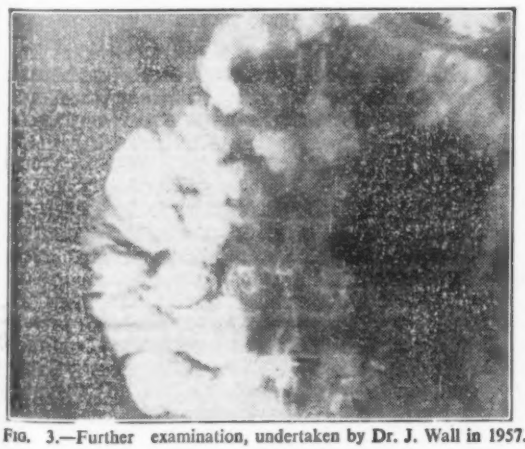

FIG. 3.—Further examination, undertaken by Dr. J. Wall in 1957. (D. B. F.) massive diverticulosis localized to the proximal

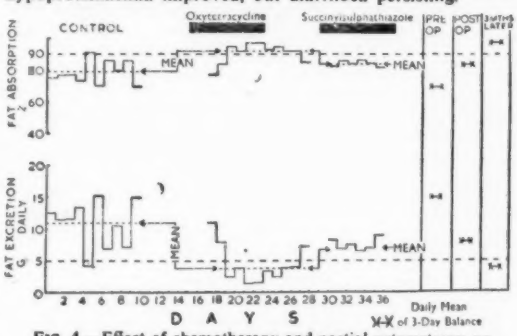

FIG. 4.—Effect of chemotherapy and partial enterectomy on steatorrhoea associated with jejunal diverticulosis.

Ankle oedema recurred shortly after discharge and diarrhoea again became severe, necessitating readmissions to hospital in May and in July, 1957. Improvement followed a high-protein low-salt diet and the use of mersalyl injections twice weekly. The oedema could not be wholly attributed to hypoproteinaemia as plasma protein levels had continued to improve and the blood count remained satisfactory; bilateral varicose veins probably contributed to this condition. He was again discharged, to continue diet, diuretics, and injections of cyanocobalamin at home.

By May, 1957, although the patient was much improved, his diarrhoea remained uncontrolled and a definite diagnosis had not been established. Pernicious anaemia was suggested from the haematological findings, low serum cyanocobalamin levels, achlorhydria, and the apparent response to cyanocobalamin injections. Against the diagnosis were the presence of the diverticula with steatorrhoea, the gastroscopic findings, and the fact that minimal haematological improvement followed chlortetracycline therapy. The possibility of surgical excision of the diverticula was now considered. It was felt that excision would be an easy and reasonable procedure as both the diarrhoea and the haematological state appeared to improve when the diverticula were sterilized, and as they appeared to arise high in the jejunum comparatively close together (Fig. 3).

Pre-operative Assessments

It was first established that chemotherapy would temporarily control the steatorrhoea (Fig. 4). On a 50 g. fat diet, the daily fat content of the patient's stool was estimated over a control period of 10 days and averaged 10.5 g., representing a true steatorrhoea (79% absorption). After a week's course of oxytetracycline, 1 g. daily, fat excretion fell to an average of 1.4 g. daily but rose again as oxytetracycline was discontinued. Succinylsulphathiazole in doses of 4 g. daily for 10 days did not abolish steatorrhoea, for in this period his stools contained on an average 7.5 g. daily (85% absorption). Immediately before operation, in September, 1957, fat absorption over a three-day period was 70%.

In an attempt to distinguish Addisonian anaemia and malabsorption clearly, and also to assess the effect of operation on the haematological picture, cyanocobalamin therapy was suspended in May, 1957, when the haemoglobin was 97% (14.3 g./100 ml.) and the red-cell count 4,900,000. At this time the serum cyanocobalamin level was 356 $\mu\mu$g./ml.; two months later this had fallen to 225 $\mu\mu$g./ml., and in August, 1957, to 128 $\mu\mu$g./ml., with slight deterioration in the haematological picture (haemoglobin, 80% (11.8 g./100 ml.), red-cell count 4,300,000). At laparotomy

3 ft. (90 cm.) of the jejunum was found extending from the duodeno-jejunal flexure downwards. Resection was easily accomplished and end-to-end anastomosis performed.

The pathological specimen removed (shown in Fig. 5) was described as follows (J. A. D.). "A loop of small intestine 70 cm. long. On the mesenteric border numerous diverticula are present, and project into the mesentery so that they bulge between the vessels of the mesenteric arcade. The diverticula measure from a minute dimension up to 5 cm. in diameter and communicate with the small bowel via a large orifice up to 2 cm. in diameter. *Histology:* These diverticula are lined with glandular epithelium of the small intestinal type and there is muscle in the wall corresponding to the various coats of the small intestine. The nerve plexuses are present. The only point of distinction is that the mucosa is smoothly applied around the diverticulum and is not thrown into folds as in the small bowel."

FIG. 5.—Operative specimen of a loop of small intestine.

Although organisms resembling normal intestinal flora were cultured from the diverticula, experiments to establish their nature and ability to utilize cyanocobalamin proved inconclusive.

Effects of Operation

The patient stood the operation well, transfusion was not required, and post-operative complications did not occur. After the operation his stools became formed for the first time in five years and have remained so, two stools being passed daily. He was immensely satisfied with the operative outcome. It was thought desirable that a full year should elapse before results of the operation were assessed to confirm that the initial favourable effects would be lasting.

The haematological effects are summarized in Fig. 2. As already stated, after the suspension of cyanocobalamin injections the serum levels of the vitamin fell, reaching 128 $\mu\mu$g./ml., the haemoglobin from 97% (14.3 g./100 ml.) to 80% (11.8 g./100 ml.), and the red-cell count from 4,900,000 to 4,300,000 in the same period. After excision of the diverticula the serum cyanocobalamin level rose spontaneously without haematinics to 288 $\mu\mu$g./ml. and 12 months after operation had reached 360 $\mu\mu$g./ml. All these are within the normal range, and this fact provides evidence that the diverticula had in some way interfered with absorption of the vitamin. After an initial dramatic improvement in haemoglobin and red-cell counts a month after operation to 98.5% (14.6 g./100 ml.) and 4,900,000 respectively, the long-term effects have been less well sustained, the haemoglobin varying between 78% and 86% (11.5 and 12.7 g./100 ml.) and the red-cell count between 4,200,000 and 4,600,000. Although initially a histamine-fast achlorhydria had been demonstrated without pepsin secretion, repeat analysis four months after operation revealed normal acidity and adequate peptic activity: an example of reversible achlorhydria complicating anaemia (Watkinson, 1959).

The effects of operation on the steatorrhoea are shown in Fig. 4: immediately before operation a three-day fat balance had shown only 70% absorption of the 50 g. fat diet given. After operation the stools became formed and diarrhoea had not recurred in the succeeding 12 months. However, one month after operation balance studies showed that, although fat absorption had been improved to 86%, steatorrhoea had not been completely abolished. A further balance performed three months after operation showed fat absorption to be now normal at 96% of the administered fat; a smaller improvement in folic acid absorption had also occurred.

Discussion

The syndrome of jejunal diverticulosis with steatorrhoea and a megaloblastic anaemia is rare. Only 16 patients with the complete syndrome have been reported in the literature, but a further five patients without anaemia are also recorded. In five instances complications of previous operative procedures, such as gastrectomy, fistulae, and blind loop and intestinal resection, might have contributed towards the production of macrocytic anaemia or steatorrhoea. Bone-marrow studies were performed in 17 patients and found to be megaloblastic in 16. Subacute combined degeneration, histamine-fast achlorhydria, and jaundice had been reported to complicate the syndrome, while liver extract or cyanocobalamin administered parenterally proved effective in most instances.

The similarity of the anaemia complicating jejunal diverticulosis to Addisonian anaemia raises the diagnostic problem, as in our patient, of whether coincident pernicious anaemia is present in a patient with diverticulosis. Such an association can usually be excluded by the demonstration of free hydrochloric acid on gastric analysis, acid being present in 11 of 17 reported so examined. In two of the six with achlorhydria coincident pernicious anaemia could not be positively excluded (Taylor, 1930; Townsend and Cameron, 1957), differentiation in the remaining patients proving extremely difficult. In our patient a true histamine-fast achlorhydria without pepsin secretion initially suggested pernicious anaemia, and gastric biopsy findings were equivocal. While in some young subjects with pernicious anaemia acid secretion has returned after cyanocobalamin therapy (Magnus, 1958), such a state of affairs has not been reported in middle-aged or elderly subjects, and at this age normal gastroscopic appearances and the return of acid secretion after the anaemia had been corrected tend to refute the diagnosis.

Another point of differentiation from Addisonian anaemia is in the presence of steatorrhoea found in 13 of the previously reported cases. This was a prominent feature of our patient. Again the chance association of jejunal diverticulosis with idiopathic steatorrhoea must be borne in mind. Idiopathic steatorrhoea is an inborn gluten intolerance usually affecting young subjects and producing multiple malabsorptive defects. In the reported cases of diverticulosis steatorrhoea is usually of abrupt onset in elderly people, often accommpanied by obstructive symptoms, while steatorrhoea and other malabsorptive defects were usually mild. Oral glucose-tolerance tests, as in our patient, gave normal results, and the radiological findings were quite dissimilar from the sprue syndrome. Abolition of the steatorrhoea by sterilization of the bowel contents with antibiotics can usually be demonstrated, as in our patient.

Some similarity can be drawn between jejunal diverticulosis and tropical sprue in that both conditions are of abrupt onset, possibly related to changes in bacterial flora, and both improve with antibiotic treatment (French, Gaddie, and Smith, 1956). The beneficial effects of elective excision of all the diverticula on the steatorrhoea have not been previously quantitatively demonstrated, fat absorption increasing from 70% pre-operatively to 96% post-operatively. Scudamore, Hagedorn, Wollaeger, and Owen (1958), because of obstructive symptoms in one of their patients, found it necessary to excise 45 cm. of jejunum containing one large and many small jejunal diverticula, but made no observations of the effect of the operation on fat absorption.

As in other malabsorptive states, megaloblastic anaemia in jejunal diverticulosis might result from cyanocobalamin or folic acid deficiency, or from a combination of both. Absolute cyanocobalamin deficiency was demonstrated in our patient by the extremely low serum level, initially 20 $\mu\mu$g./ml., and the response to cyanocobalamin injections. There seemed to be neither tissue depletion nor defective absorption of folic acid as assessed by balance studies, though a minimal reticulocytosis followed its administration. Similar low serum cyanocobalamin levels in the syndrome were demonstrated by Badenoch and Bedford (1954) and by Spray and Witts (1958). Most of the cases reported in the literature responded to parenterally administered cyanocobalamin or liver extract, while the responses to folic acid were fewer and less well established.

The mechanism by which cyanocobalamin deficiency develops in jejunal diverticulosis has been ascribed to failure of secretion of the intrinsic factor (Castle *et al.*, 1931), to defective absorption which accompanies any steatorrhoea (Girdwood, 1953), or to competition for the vitamin by the abnormal bacterial flora and in the diverticula (Badenoch, 1958). Evidence that the third hypothesis is the likely explanation stems from the fact that sterilization of the gut with antibiotics often induces haematological improvement. However, it should be recalled that steatorrhoea is also abolished by oral antibiotics—improved intestinal absorption in part inducing haematological benefit, supporting Girdwood's hypothesis. Tests of the intestinal absorption of ^{60}Co-labelled cyanocobalamin have shown that, while the addition of excessive amounts of intrinsic factor to orally administered vitamin will improve absorption, it is normally absorbed when administered alone after previous sterilization of the gut contents by chlortetracycline (Badenoch, 1958; Scudamore *et al.*, 1958). The exact manner by which bacteria may interfere with the intestinal absorption of cyanocobalamin is unknown: stasis and prolonged retention of food within the diverticula may play a part, but why the condition should suddenly develop in diverticula known to have been present for many years, and in most instances asymptomatic, remains unsolved.

The beneficial effects of resection of the diverticula on the haematological picture have not been previously demonstrated. In the case reported by Scudamore *et al.* (1958) the absorption of ^{60}Co-labelled cyanocobalamin was not improved by resection of the diverticula, while haemoglobin levels tended to fall for the next two months, improving with cyanocobalamin therapy and antibiotics later. In our patient both blood count and serum cyanocobalamin levels improved without haematinics after operation, and improvement has been maintained.

Faced with the rare combination of megaloblastic anaemia with or without steatorrhoea, the possibility of coincident pernicious anaemia should first be excluded and may prove difficult. While test-meal findings and serum cyanocobalamin levels will be sufficient in many patients these tests may not be diagnostic and could not form a basis for differentiation in our patient. Haematological and absorptive improvements following sterilization of the gut by oral antibiotic therapy form one of the most useful diagnostic indications, and these can be beautifully demonstrated by absorption studies using ^{60}Co-labelled cyanocobalamin alone, with intrinsic factor and after oral antibiotic therapy (Halsted, Swendseid, Lewis, and Gasster, 1956). Provided the majority of diverticula are close together, surgical excision, in patients in whom medical treatment fails to effect haematological or nutritional improvement, seems a reasonable procedure and has yielded gratifying results in the case reported.

Summary

The case of a patient with the rare syndrome of massive jejunal diverticulosis with steatorrhoea and megaloblastic anaemia is described and the literature relating to the condition reviewed.

Difficulties in differentiation of this syndrome from coincident Addisonian anaemia are described. While test-meal findings, gastric biopsy, and low serum cyanocobalamin levels will usually enable distinction to be made, a firm diagnosis on these criteria was not possible in our patient initially, diagnosis being eventually made on haematological and absorptive improvements following sterilization of the gut by oral antibiotics.

Partial enterectomy, with excision of all the diverticula, induced both haematological improvement and abolished the steatorrhoea in our patient, and might be considered in other patients with this syndrome in whom medical treatment has failed.

Our thanks are due to Mr. F. J. Powell, who performed most of the biochemical tests; to Dr Winifred Mitchell for undertaking the folic-acid-balance tests; and to Dr W. Goldie and Dr I R Fountain for their help at all stages of this investigation.

References

Badenoch, J. (1958). In *Modern Trends in Gastro-enterology* (2nd series) edited by F Avery Jones, p. 231. Butterworth, London.
— and Bedford, P. D. (1954). *Quart. J. Med.*, **23**, 462.
— — and Evans, J. R. (1955). Ibid., **24**, 321.
Blachford, R. D., and Dawson, D. W. (1956). *Brit. med. J.*, **1**, 1407.
Castle, W. B., Heath, C. W., and Strauss, M. B. (1931). *Amer. J. med. Sci.*, **182**, 741.
Dick, A. P. (1955). *Brit. med. J.*, **1**, 145.
Dossett, J. A., and Droller, H. (1959). In press.
French, J. M., Gaddie, R., and Smith, N. M. (1956). *Quart. J. Med.*, **25**, 333.
Gellman, D. D. (1956). *Lancet*, **2**, 873.
Girdwood, R. (1953). Ibid., **2**, 53.
Halsted, J. A., Swendseid, M. E., Lewis, P. M., and Gasster, M. (1956). *Gastroenterology*, **30**, 21.
Hutner, S. H., Bach, M. K., and Ross, G. I. M. (1956). *J. Protozool.*, **3**, 101.
Krevans, J. R., Conley, C. L., and Sachs, M. (1954). *J. clin. Invest.*, **33**, 949.
Magnus, H. A. (1958). *J. clin. Path.*, **11**, 289.
Montuschi, E. (1949). *Proc. roy. Soc. Med.*, **42**, 868.
Scudamore, H. H., Hagedorn, A. B., Wollaeger, E. E., and Owen, C. A. (1958). *Gastroenterology*, **34**, 62.
Spang, A. (1954). *Fortschr. Röntgenstr.*, **81**, 55.
Spray, G. H., and Witts, L. J. (1958). *Brit. med. J.*, **1**, 295.
Taylor, G. W. (1930). *New Engl. J. Med.*, **202**, 269.
Townsend, S. R., and Cameron, D. G. (1957). *Amer. J. Med.*, **23**, 668.
Watkinson, G. (1959). In press.
Zingg, W. (1950). *Gastroenterologia (Basel)*, **75**, 352.

PSEUDO B: AN ACQUIRED GROUP ANTIGEN

BY

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A number of blood samples possessing weak B antigens have been reported (Mäkelä and Mäkelä, 1955; Moullec *et al.*, 1955; Yokoyama *et al.*, 1957; Boorman and Zeitlin 1958; Levine *et al.*, 1958). Family studies on some of these have shown that the particular antigen was inherited in a recognizable way. The purpose of this report is to present evidence for the existence of an additional type of weak B antigen developing *de novo* as a temporary acquired character.

Case Report (and Materials)

Miss X, aged 64, a mild schizophrenic, was admitted to a general hospital for resection of a carcinoma of the upper part of the sigmoid colon. The diagnosis was confirmed by histological examination of the tumour.

Difficulty was experienced in determining her ABO group during routine pre-operative tests (sample 1). Her cells grouped as AB with a weakly reacting B component, while her serum contained anti-B agglutinins. The saliva contained no B substance. Blood and Saliva taken a week later showed exactly the same serological characteristics (sample 2). Between the taking of the two samples, one pint (500 ml.) of group A Rh-negative blood was transfused. Ten weeks after the collection of the second sample the patient died and a sample of blood was obtained by cardiac puncture three and a half days after death (sample 3). Miss X was not a twin. She had one brother and one sister, both of whom were tested. Her parents were dead.

Methods.—A standard tube technique was employed throughout using 2% cell suspensions. Unless otherwise stated, the incubation periods were two hours at room temperature (18° C.). Titration results were scored in the manner recommended by Race and Sanger (1958) (+++=10, ++=8, +=5, ±=3, w=2, −=0). Most of the tests were completed within two weeks of collection of the samples. Saliva and serum were stored deep-frozen and red cells were frozen in glycerol.

Results: Samples 1 and 2

Cells

As stated above, the cells gave unusual reactions within the ABO group system. Other groups were: cde/cde, MN, S+, P+(weak), Lu^a neg. Kell neg. Lewis (a−), Duffy (Fy^a). The direct anti-human-globulin test was negative.

Tests with anti-A, anti-A$_1$, and anti-A+B were strongly positive with very few free cells. Reactions with antiH (extract of *Ulex europaeus*) were weakly positive. Twelve anti-B testing sera at room temperature all gave positive macroscopic agglutination with many free cells. The agglutinated cells were separated by shaking with isotonic group B saliva, washed, and resuspended in saline. Apart from their behaviour with anti-B, they were identical with the supernatant free cells. When the supernatant cells were retested with six anti-B sera at 4° C., additional weak agglutination occurred. It seemed that most of the cells contained the weak "B" type antigen, possibly in varying amounts.

The cells were agglutinated by a rabbit anti-B serum, and tests with 47 unselected human anti-B sera at 12° C. were all positive, the strength of the reactions varying considerably.

Anti-B testing serum was then diluted 1:2 with saline, and various salivas were similarly diluted and added to it. After 15 minutes at room temperature Miss X cells and B cells were added in parallel.

TABLE I.—*Inhibition by Saliva of the Reaction Between Anti-B Serum and Miss X Cells*

	One Volume of Anti-B Serum				
	Saliva				
	AB Secretor	A Secretor	B Secretor	O Secretor	O Non-secretor
Miss X cells	−	++	−	++	++
B cells ..	−	+++	−	+++	+++

As can be seen from Table I, the reaction between Miss X cells and anti-B serum was inhibited by B-containing saliva only.

Titrations with Miss X cells and anti-B sera at various temperatures showed that her cells scored about half that of the control B cells and that reactions were maximal at low temperatures. High titre anti-A+B serum, completely absorbed with pooled group A cells, still reacted with B cells and Miss X cells.

Miss X cells together with A and B control cells were used to absorb a powerful anti-B serum. After each of three absorptions, the anti-B content of the supernatant serum was determined by titration against pooled B cells.

TABLE II.—*Results of Absorption of Anti-B Serum with Miss X Cells and Control Cells*

	Score		
	One Absorption	Two Absorptions	Three Absorptions
Anti-B after absorption with B cells	3	—	—
Anti-B after absorption with A cells	79	67	59
Anti-B after absorption with Miss X cells ..	72	57	49

Anti-B before absorption, score 94.

After the first absorption the sera (Table II) were examined. Absorption of the anti-B serum with B cells or Miss X cells removed the antibody for Miss X cells. Absorption with group A cells did not.

Absorption and elution tests were then made between Miss X cells and a pool of six anti-B sera. Equal volumes of cells and serum were used, and absorption at 4° C. for three hours was followed by washing four times in cold saline and elution of the antibody into saline at 56° C. The antibody dissociated more readily than with normal B cells at this temperature and a potent eluate was obtained.

From Table III it can be seen that the eluate reacts with B-containing cells only and is inhibited by B-containing saliva only.

TABLE III.—*Reactions of Eluted Antibody from Miss X Cells After Anti-B Absorption*

	A Cells	B Cells	O Cells	AB Cells
Eluate	−	++	−	++
Eluate + B saliva	−	−	−	−
,, +A ,,	−	++	−	++

When agglutinated cells were shaken with various salivas the agglutination could be dispersed only in the presence of B-containing saliva.

After absorption with Miss X cells, the anti-B agglutinins in the pooled sera were titrated and scored 74 (titre 1:256). The absorption was then repeated with a fresh sample of Miss X cells. An eluate prepared from these cells contained only a trace of anti-B antibody (± reaction).

These absorption and elution tests show conclusively that Miss X cells react specifically with anti-B sera. However, the cells appear to react with only a certain fraction of the anti-B, and once this fraction has been absorbed, even though strong anti-B agglutinins remain in the serum, no further reaction with Miss X cells takes place.

The atypical B antigen appeared to be quite stable and stored satisfactorily in glycerol at −20° C. Washing the cells 10 times in saline at 37° C. did not weaken the reaction.

Miss X cells were tested with 40 group AB sera, and and 9 of these caused macroscopic agglutination. The addition of saliva of any group did not inhibit the reaction, and the antibody could be absorbed by, and eluted from, Miss X cells or "T" activated cells only. Tests at different temperatures showed that the antibody had a thermal optimum of 4° C. and was not inhibited by inactivation at 56° C. for 30 minutes. The positive sera contained no anti-A_1 or other irregular antibodies. Ficin treatment of Miss X cells increased the strength and numbers of reactions obtained. Miss X cells, therefore, in addition to possessing a weak B antigen, were polyagglutinable.

Comparative absorptions and titrations, using naturally occurring and immune anti-A antibodies, showed that Miss X cells contained a normal A_1 antigen.

Serum

Miss X serum (samples 1 and 2) contained anti-B agglutinins. Apart from a very weak cold antibody (see below), no other antibodies could be detected. Titrations against pooled B cells at different temperatures showed that the anti-B had a thermal optimum of 4° C., at which temperature the titre was 1:64 (score 51). At 37° C. it had a titre of 1:8 (score 24). No anti-B haemolysins could be detected, and the antibody could be completely neutralized by group B or AB saliva but not by group O or A. After partial neutralization with B saliva, no incomplete anti-B agglutinins could be detected by the indirect anti-human-globulin test. The serum was tested against 25 random sampled group B donors and on three occasions against pooled B cells (30 blood samples to each pool). In each instance strong positive reactions were obtained with very few free cells. In sport, the antibody gave the reactions of a normal anti-B agglutinin with no immune characteristics.

Miss X serum has been tested against her own cells in saline at 4° C., 12° C., room temperature, and 37° C., and in albumin and by indirect anti-globulin and enzyme (ficin) techniques at 37° C. At 4° C. a very weak non-specific cold agglutinin could be detected. After absorption of this antibody with group O cells, tests between her own serum and cells were negative. As previously mentioned, the direct anti-globulin test on Miss X cells was negative.

After absorption of Miss X own anti-B agglutinin, attempts were made by inhibition techniques to demonstrate B substance in the serum. The results were inconclusive. Group A cells suspended in the serum for three hours at 37° C. failed to absorb any B substance.

Saliva

Miss X saliva was boiled in a water-bath and examined quantitatively for the presence of A, B, and H substances. A and H substances were present in about averagte amounts; no water-soluble B substance could be detected. Her saliva had no inhibitory effect on serial dilutions of anti-B serum (Table IV).

TABLE IV.—*Test for B Substance in Miss X Saliva*

	Group B Cells Added								
	Anti-B Dilutions								
	1	2	4	8	16	32	64	128	256
1 volume B saliva to each	±	−	−	−	−	−	−	−	−
1 volume A saliva to each	+++	+++	+++	++	+	±	±	−	−
1 volume Miss X saliva to each ..	+++	+++	+++	+++	++	++	+	±	−
1 volume saline to each ..	+++	+++	+++	+++	++	++	+	±	−

Miss X saliva did not inhibit her own anti-B antibody or the reaction between her cells and certain AB sera.

Results: Sample 3 (Post Mortem)

The third sample consisted of about 10 ml. of cells and serum obtained by cardiac puncture three and a half days after death (10 weeks after sample 2). It was in good condition and showed no haemolysis.

Cells

Differences from the previous samples were found in the ABO group. The remaining genotype was repeated and found to be unchanged. Ten anti-B grouping sera were tested separately against the cells from the post-mortem sample and cells from the original sample (stored frozen) in the parallel (Table V).

TABLE V.—*Comparison of Reaction with Anti-B Sera on Samples 1 and 3*

	Anti-B Sera Numbers									
	1	2	3	4	5	6	7	8	9	10
Miss X cells (sample 1) ..	+++	++	++	+++	+++	+	++	+	++	+++
Miss X cells (sample 3) ..	±	−	−	±	−	±	+	−	±	−

The original cell sample still gave good macroscopic agglutination, but the reactions with the post-mortem sample were almost negative. Careful microscopical examination, however, showed an occasional agglutinate of three or four cells with some of the sera. These tests were repeated with the addition of group B saliva. Some of the weak reactions were then inhibited and it was concluded that the weak agglutination was due to: (1) polyagglutination, and (2) a few surviving weak B cells. Tests with rabbit anti-B serum were negative. Absorption and elution tests showed that the cells of the post-mortem sample did not absorb the human anti-B component specific for the cells of the earlier samples.

Tests against selected AB sera showed that the post-mortem cells were still polyagglutinable, but the results were, on the whole, weaker than those obtained with the original sample.

The possibility of deterioration of group antigens in the post-mortem sample was considered. Repeated comparative titrations, however, between the cells of samples 1 and 3, using anti-A, anti-H, and anti-P (selected because of the previous weak reactions) showed the same results.

The serological evidence suggests that the group antigens in the post-mortem sample were well preserved. Previous tests on the initial sample had shown that the weak B antigen was stable. The negative reactions with anti-B serum on the post-mortem sample are therefore unlikely to be due simply to deterioration.

It is probable that the weak B antigen in the earlier samples had appeared as an acquired character. An attempt was therefore made to reproduce the phenomenon *in vitro* on the post-mortem cells by exposing them to the action of enzymes. The cells were incubated for two hours with twice the volume of a powerful bacterial "T" activating enzyme. After one wash in saline the cells were left in two volumes of a 1:6 dilution of the same enzyme at 4° C. for a further 15 hours and were then washed three times in saline. Two anti-B testing sera were pooled and absorption tests made using the above cells and untreated post-mortem cells in parallel. Absorption at 4° C. for two hours was followed by four washes in cold saline and elution into saline at 56° C. The experiment was successful and, as can be seen from Table VI, the enzyme-modified cells yielded on elution a potent anti-B agglutinin. The anti-B serum that had been absorbed with the modified cells agglutinated other B cells, but failed to react with cells from samples 1 and 2.

TABLE VI.—*Reactions of Eluate from Enzyme-modified Cells and Unmodified Cells from Sample 3 After Anti-B Absorptions*

Eluate from	A Cells	B Cells	AB Cells	O Cells
Untreated cells ..	–	–	–	–
Enzyme-modified cells	–	+++	+++	–
Enzyme-modified cells + A saliva	–	+++	+++	–
Enzyme-modified cells + B saliva ..	–	–	–	–

Further tests then showed that this phenomenon was not peculiar to the cells of Miss X. Two normal group A_1 cell samples were exposed to the same enzyme under the same conditions. Absorption and elution tests, as above, showed that these cells also developed a B antigen. It was found, however, that Miss X cells from sample 1 were agglutinated by anti-B serum absorbed with the normal "pseudo B" cells, and, conversely, the eluate from these cells failed to react with Miss X cells. Clearly more than one type of "pseudo B" antigen can develop, and it is probable that Miss X post-mortem cells, already partially modified *in vivo*, developed both types of pseudo B antigen on further modification. Investigations into the reactions of these pseudo B antigens are continuing.

Serum

Anti-B agglutinins were present in the serum. The antibody had the same characteristics as in the previous samples. As before, no immune anti-B could be detected and the antibody was completely inhibited by B but not by A saliva. The serum was tested against cells from samples 1 and 2 and also cells from the post-mortem sample at various temperatures. All the tests were negative, as also was the direct anti-human-globulin test on the post-mortem cells.

Family Study

As mentioned previously, the propositus had one brother and one sister, both of whom were tested. Her parents were dead. The brother and sister were fit and were both group A_1. Tests with six anti-B sera against their cells were negative and the cells were not polyagglutinable. The anti-B agglutinins from both their bloods reacted with the weak B antigen in the cells of Miss X.

Discussion

Miss X cells contain a weak B antigen which reacts with only a certain component of anti-B sera. Anti-titrations against her cells show that this component is most active at low temperatures and presumably naturally occurring. Weak reactions with anti-B serum on a sample of cells can be explained in a number of ways. The most obvious way is by transfusion with group AB blood. Akeroyd and O'Brien (1958) have shown that small numbers of AB cells may survive for some weeks after transfusion into group A individuals. In this case the only transfusion given was one pint (500 ml.) of group A blood after the weak B. antigen had already been detected.

The large number of free cells in the original ABO group suggested the possibility of a chimera. Miss X cells, however, cannot be clearly differentiated into two types. The serological evidence suggests varying amounts of the antigen in most of her cells. Furthermore, she is not, so far as is known, a twin A chimera was finally excluded by the disappearanme of most of the B-containing cells.

van Loghem *et al.* 1957) and Stratton *et al.* (1958) have reported cases in which a presumably normal A antigen has become progressively weaker. Neither case secreted A or H substances, nor developed anti-A antibodies. The pattern is clearly quite distinct from that occurring in Miss X.

Weak B antigens with anti-B in the serum have been reported by Mäkelä and Mäkelä (1955) and by Boorman and Zeitlin (1958). B substance was present in the saliva in both instances. Moullec *et al.* (1955) have described a family with weak cellular B antigens (B_3), but no B substance in the saliva or anti-B in the serum. Levine *et al.* (1958) have described a very weak B antigen (B_w) in the cells of a family who secrete B substance in their saliva, and Yokoyama *et al.* (1957) have described what may be a weaker variety of the same antigen (B_x).

The serological results on Miss X differ from these cases in detail, apart from the disappearance of her B-containing cells.

The experimental evidence proves that the B antigen on Miss X cells could have developed as an acquired character by the action of some agent on the group substance of her cells. Enzymic action can be shown to have taken place by the fact that her cells are polyagglutinable. Furthermore, the *in vitro* experiments, using both the post-mortem cells and normal group A_1 cells, show that under the influence of certain enzymes a week B antigen can be made to appear. Iseki and Masaki (1953) have already shown by *in vitro* experiments that certain bacterial enzymes may modify A and O group substances and in doing so reverse their specificity. It is our opinion that *in vivo* modification of the group substance in a similar way has caused the development of the B antigen in Miss X cells.

The absence of B substance from the saliva of Miss X, together with the eventual disappearance of nearly all of the cells possessing the weak B antigen, are facts which support the hypothesis of an acquired B antigen. The family study, unfortunately, contributes very little to the investigation beyond establishing that neither the brother nor sister possesses the same antigen.

If the idea of an acquired B antigen is accepted, then the reactions of Miss X's anti-B agglutinins become interesting. It has been shown that her cells react with a specific component of anti-B sera. The absence of any reactions between her cells and her own serum suggests strongly that her serum lacks this specific component. Two possible explanations for the absence of this fraction must be considered: (1) *in vivo* absorption by her own cells, and (2) depression of her antibody-producing mechanism.

Miss X cells cannot be shown to be sensitized or coated with antibody by any technique. Furthermore, the post-mortem serum fails to react with the cells in the original sample. From this it is clear that the post-mortem serum still lacks the fraction that would agglutinate her own cells. As the post-mortem sample is almost free from weak B cells that could absorb her own antibody, it follows that auto-absorption is unlikely to be the explanation of the missing fraction. It appears most probable that her red cells have been modified and acquired a B antigen. This antigen in turn has caused a modification of her anti-B agglutinins, thus preventing a reaction with her own cells.

The chimeras that have been reported (Dunsford *et al.*, 1953; Booth *et al.*, 1957; Nicholas *et al.*, 1957) show that exposure to a foreign antigen early in foetal life can inhibit antibody production thereafter. Dunsford and Stacey (1957) have reported partial breakdown of this antibody suppression in a chimera possessing A and O red cells. Anti-A agglutinins developed in this case that were not, however, auto-agglutinating. It would appear that Miss X, whose case is here reported, confirms their supposition of immunological tolerance and establishes that foreign antigens may be tolerated, even in the presence of "homologous" antibody, providing the "foreign" antigen is present in the individual's own cells.

Summary

A new type of weakly reacting B antigen is described. B substance was absent from the saliva and anti-B agglutinins were present in the serum. Serological evidence is given to show that this antigen probably developed as an acquired character, and a technique is described by which a B antigen can be produced *in vitro* in group A_1 cells. The anti-B agglutinins in the serum did not react with the acquired weak B antigen in the cells, and possible causes for this are discussed.

We are grateful to Dr. R. R. Race, from whom we obtained the "T" activating enzyme, to Mr. D. E. Gurney for his co-operation in the collection of the post-mortem sample, and to Miss Jane Mears for her technical assistance during the investigation.

REFERENCES

Akeroyd, J. H., and O'Brien, W. A. (1958). *Vox Sang. (Basel)*, **3**, 330.
Boorman, K. E., and Zeitlin, R. A. (1958). *Report to VII Congress of the Society of Blood Transfusion*, p. 178.
Booth, P. B., Plaut, G., James, J. D., Ikin, E. W., Moores, P., Sanger, R., and Race, R. R. (1957). *Brit. med. J.*, **1**, 1456.
Dunsford, I., Bowley, C. C., Hutchinson, A. M., Thompson, J. S., Sanger, R., and Race, R. R. (1953). Ibid., **2**, 81.
—— and Stacey, S. M. (1957). *Vox Sang. (Basel)*, **2**, 414.
Iseki, S., and Masaki, S. (1953). *Proc. Jap. Acad.*, **29**, 460.
Levine, P., Celano, M. J., and Griset, I. (1958). *Proc. VI Congr. Int. Soc. Blood Transfusion*, p. 132.
Loghem, J. J. van, Dorfmeier, H., and Hart, M. van der (1957). *Vox Sang. (Basel)*, **2**, 16.
Mäkelä, O., and Mäkelä, P. (1955). *Ann. Med. exp. Fenn.*, **33**, 33.
Moullec, J., Sutton, E., and Burgada, M. (1955). *Rev. Hémat.*, **10**, 574.
Nicholas, J. W., Jenkins, W. J., and Marsh, W. L. (1957). *Brit. med. J.*, **1**, 1458.
Race, R. R., and Sanger, R. (1958). *Blood Groups in Man*, 3rd *ed.*, p. 246. Blackwell, Oxford.
Stratton, F., Renton, P. H., and Hancock, J. A. (1958). *Nature (Lond.)*, **181**, 62.
Yokoyama, M., Stacey, S. M., and Dunsford, I. (1957). *Vox Sang. (Basel)*, **2**, 348.

PURPURA IN KWASHIORKOR

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Purpura is a well-known though uncommon clinical finding in children suffering from kwashiorkor (malignant malnutrition, infantile pellagra), the haemorrhagic spots in these patients occurring principally over the clavicles, lower abdomen, and groin, occasionally coalescing into large purplish blotches. It is briefly referred to by some authors in the discussion of the dermatosis of malnutrition (Hanafy, 1948; Achar, 1950; Trowell *et al.*, 1954), but little work has been done to elucidate the cause of the purpuric eruption, and for the most part it appears to have been accepted as a manifestation of rupture of fragile vessels in poorly nourished tissues.

At this hospital we see from 600 to 800 cases of severe kwashiorkor annually, and most of these patients are between 6 months and 3 years old. About 80% of these children suffer from primary malnutrition, being weaned on to a diet of maize porridge and water at an early age. In the remaining 20% chronic debilitating diseases, most commonly tuberculosis and salmonellosis, are present in addition to malnutrition. Parasitic diseases such as malaria and hookworm are not endemic in this area. Mild iron deficiencies and megaloblastic anaemia with haemoglobin levels of about 8 g./100 ml. are not uncommon, but purpura is relatively rare, being seen in 3–5% of patients suffering from kwashiorkor.

It has been our impression that the purpura of malnutrition is rarely associated with obvious haematological defects, but that there appears to be an undue preponderance of tuberculosis and salmonellosis in such patients. It was with a view to elucidating this observation that we undertook the following investigation.

Materials and Methods

We investigated 23 severely malnourished children suffering from purpura who were admitted to our wards over a period of nine months. All suffered from severe malnutrition with evidence of nutritional oedema or acute nutritional dermatosis or both.

The following investigations were carried out in all cases: the bleeding-time was determined by Duke's method and the clotting-time by the method of Lee and White; haemoglobin estimation, prothrombin index (Quick one-stage method), and bile and broth cultures were performed, using venous blood; all patients were subjected to tuberculin-testing with second-strength purified protein derivative, and their chests were radiographed; rectal swabs were taken and cultured for

Purpura in Kwashiorkor

Case No.	Age (Mths)	Sex	Weight lb.	Weight kg.	Hb (g./100 ml.)	Platelets (per c.mm.)	Prothrombin Index %	Bleeding-time (Minutes)	Clotting-time (Minutes)	Pathogens in Stools	Blood Culture	Mantoux Test	Chest X-ray	Bone Marrow	Summary of Diagnosis
1	13	M	14	6·4	6·4	>150,000	100	4	5	Nil	Salm.	Neg.	Normal	—	K. and S.
2	22	M	23	10·4	5·4	>150,000	90	2	4	,,	Neg.	Pos.	Tuberculous broncho-pneumonia	—	K. and P.T.
3	15	M	15	6·8	11·7	>150,000	84	2	4½	,,	,,	,,	,, ,,	—	,, ,,
4	12	M	12	5·4	10·6	>150,000	91	2	3	,,	,,	Neg.	Normal ,,	—	Kwashiorkor
5	8	M	8½	3·9	10·8	>150,000	100	1	4	,,	,,	,,	,,	—	,, ,,
6	23	M	15	6·8	9·4	>150,000	95	1	2½	Salm.	,,	,,	,,	—	K. and S.
7	19	M	17	7·7	10·6	>150,000	54	4	4	Nil	,,	,,	,,	—	Kwashiorkor
8	4	M	5½	2·5	15·2	>150,000	95	1½	3½	Salm.	,,	,,	,,	—	K. and S.
9	18	F	19	8·6	11·9	20,000	68	10	4	Nil	,,	,,	,,	Few mega-karyocytes	K. and Thr.
10	7	M	9	4·1	8·9	>150,000	63	5	5	,,	,,	,,	,,	—	Kwashiorkor
11	30	F	25	11·3	4·0	25,000	95	9	3	,,	,,	,,	,,	Few mega-karyocytes	K. and Thr.
12	15	M	13	5·9	8·0	>150,000	93	1½	4	,,	,,	Pos.	Tuberculous broncho-pneumonia	—	K. and P.T.
13	8	M	10	4·5	11·2	>150,000	80	4	5	,,	Salm.	Neg.	Normal	—	K. and S.
14	8	M	11	5·0	13·1	>150,000	74	3	4½	Salm.	Neg.	,,	,,	—	,, ,,
15	14	F	7½	3·4	9·4	>150,000	62	2	2	Nil	Salm.	,,	,,	—	,, ,,
16	13	F	11	5·0	11·5	>150,000	68	2	2½	,,	Neg.	,,	,,	—	Kwashiorkor
17	14	M	15	6·8	11·4	>150,000	78	1½	5	,,	,,	Pos.	Miliary tuberculosis	—	K. and M.T.
18	24	M	20	9·1	10·1	>150,000	73	2½	3	,,	Salm.	Neg.	Normal	—	K. and S.
19	60	F	26	11·8	9·2	>150,000	92	1½	3	,,	Neg.	Pos.	Tuberculous broncho-pneumonia	—	K. and P.T.
20	36	M	20	9·1	9·5	>150,000	63	2	2	,,	,,	,,	Miliary tuberculosis	—	K. and M.T.
21	24	M	17	7·7	9·9	>150,000	74	3	2	Salm.	,,	Neg.	Normal	—	K. and S.
22	10	M	10	4·5	10·2	>150,000	93	2½	4	Nil	,,	Pos.	Tuberculous broncho-pneumonia	—	K. and P.T.
23	18	M	15	6·8	8·7	>150,000	76	3	3	,,	,,	,,	,, ,,	—	,, ,,

K.=Kwashiorkor. M.T.=Miliary tuberculosis. P.T.=Pulmonary tuberculosis. S.=Salmonellosis. Thr.=Thrombocytopenia.

pathogens; iliac crest bone-marrow punctures were carried out in two patients in whom platelet deficiencies were found.

Results of Investigation

The age of the patients in this investigation ranged from 5 months to 8 years; however, 21 of the 23 were from 7 months to 3 years old (see Table). There were 18 males and 5 females. All were severely malnourished, 13 were oedematous, and 17 had acute nutritional dermatosis; 10 were severely wasted and 6 had marked hepatomegaly.

The following haematological abnormalities were the only ones observed in this series. Bleeding-times were abnormally prolonged in two patients, with associated thrombocytopenia. Both had hypoplasia of the bone marrow with very few megakaryocytes. One of these children had received chloramphenicol previously. The marrow of one child returned to normal after a prolonged stay in hospital. The other child died of cerebral haemorrhage.

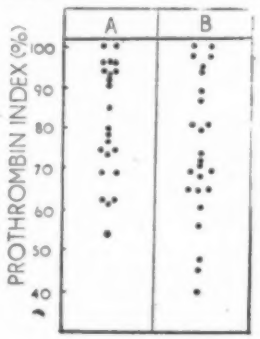
In the remaining 21 cases bleeding-times and platelet counts were normal; clotting-times were normal in all 23 cases. Prothrombin indices were less than 100% in 21 cases, the lowest level being 54%.

Evidence of associated infection with *Mycobacterium tuberculosis* or salmonellae was found in 16 of the 23 patients. Eight of these had tuberculosis, with positive tuberculin tests and active pulmonary lesions on *x*-ray examination, two being miliary in type. In the remaining eight patients, pathogens of the *Salmonella* group were isolated—four on blood culture and four in cultures from rectal swabs. Those isolated on blood culture were *Salm. typhosa*, *Salm. typhimurium*, Salm. San Diego, and Salm. Adelaide; those isolated on rectal swab culture were Salm. Kentucky, Salm. Johannesburg, Salm. Aberdeen, and Salm. Newport.

No treatment had been given to the patients with tuberculosis or salmonellosis before the purpuric rash was observed. Of the total 23 children investigated, 7 died.

Discussion

In only 2 of the 23 patients suffering from kwashiorkor with purpura was there any obvious haematological abnormality to explain the bleeding phenomenon. These were the two children with thrombocytopenia due to bone-marrow hypoplasia. In one of these, hypoplasia was probably due to the chloramphenicol toxicity; in the other the aetiology was unknown. In all other cases drugs could be excluded as an aetiological factor. In the remaining 21 children the bleeding- and clotting-times were within normal limits, platelet counts were normal, and the only abnormality detected was moderate depression of the prothrombin index. However, the latter is the usual finding in kwashiorkor; thus in a consecutive series of 25 children suffering from severe kwashiorkor but without purpura the prothrombin index was equally depressed (see Fig.). Merskey and Hansen (1955),



Prothrombin indices of 23 cases of purpura associated with kwashiorkor (A) and of 25 consecutive cases of kwashiorkor without evidence of purpura (B).

investigating purpura in kwashiorkor, found that the prothrombin index was almost invariably reduced, this reduction apparently being due to deficiency of factor VII or prothrombin itself.

The striking feature in our investigation was the high incidence of associated tuberculosis and salmonellosis. Among our admissions of kwashiorkor in 1956 there were only 8% with salmonellosis and 10% with pulmonary tuberculosis. In the present series, 16 of 23 (70%) patients had severe pulmonary tuberculosis or salmonella septicaemia or enterocolitis. This confirms our previous clinical observations extending over several years and strongly suggests some causal relationship between the purpura of kwashiorkor and these infections.

The association of tuberculosis and purpura, mainly in adults, is well described. In most instances the tuberculosis is of the miliary type, with bone-marrow infiltration causing aplasia or myelofibrosis with thrombocytopenia (Chapman and Whorton, 1946; Crail *et al.*, 1948; Gardner and Mettier, 1949; Ellman and Johnson, 1952; Fountain, 1954). Tuberculosis as a cause of purpura, without haematological abnormalities, as in our patients, is also described. Ellman and Johnson (1952), reviewing the literature, found 46 such cases. Most of these were cases of pulmonary tuberculosis without miliary spread. These authors concluded that where purpura occurs with tuberculosis there is an aetiological relationship between the two conditions, except in a few instances where a chance association cannot be excluded. Wintrobe (1951) enumerates the tubercle bacillus as a possible exciting cause of allergic purpura. Purpura following Mantoux-testing has been described (Wright and Bacal, 1937).

There is scanty reference to the association of purpura and salmonellosis. Eisenberg *et al.* (1958), discussing clinical and microbiological aspects of salmonellosis, do not list purpura as a clinical feature. Felsen (1945) does not mention the association of purpura and salmonella enterocolitis. Septicaemia is not commonly believed to be a phase of salmonella infections apart from typhoid and typhimurium, but two of the four infections isolated on blood culture in our series were *Salm.* San Diego and *Salm.* Adelaide. It is probable that the purpura occurred as a manifestation of salmonella septicaemia. Rolleston and Molony (1912), writing on cachectic purpura in children, found an association of the purpura with "infective" diarrhoea in 11 cases. They isolated *Bacillus enteritidis* (*Salm. enteritidis* from heart blood in only one case at post-mortem examination, but suggested that cachectic purpura was commonly due to this type of haemic infection. It would appear that in our African community we may well be seeing cachectic purpura such as was seen by Rolleston and Molony in children in England during the early part of this century against a similar background of malnutrition and complicated by similar infections. Since then, however, the prognosis of "cachectic" purpura has improved. All their cases were fatal, whereas 7 of our 23 patients (30%) died. The overall mortality of kwashiorkor in our unit is 20%, and this suggests that, in kwashiorkor, purpura is an indication of poor prognosis.

Summary

An investigation into the purpura of kwashiorkor is described.

Of 23 African children investigated, only 2 had prolonged bleeding-times, thrombocytopenia, and megakaryocytopenia to explain the bleeding phenomenon. The rest had normal bleeding-times and platelet counts. All had normal clotting-times. Practically all had low prothrombin indices, but so had a control group of 25 cases of kwashiorkor without purpura.

Sixteen (70%) of the patients were found to be suffering from tuberculous or salmonella infection, an association far in excess of the overall incidence of these infections in our patients with kwashiorkor. It is felt that this suggests a causal relationship between these infections and the purpura of kwashiorkor.

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REFERENCES

Achar, S. T. (1950). *Brit. med. J.*, **1**, 701.
Chapman, C. B., and Whorton, C. M. (1946). *New Engl. J. Med.*, **235**, 239.
Crail, H. W., Alt, H. L., and Nadler, W. H. (1948). *Blood*, **3**, 1426.
Eisenberg, G. M., Brodsky, L., Weiss, W., and Flippin, H. F. (1958). *Amer. J. med. Sci.*, **235**, 497.
Ellman, P., and Johnson, J. H. P. (1952). *Brit. J. Tuberc.*, **46**, 214.
Felsen, J. (1945). *Bacillary Dysentery, Colitis, and Enteritis*. Saunders, Philadelphia.
Fountain, J. R. (1954). *Brit. med. J.*, **2**, 76.
Gardner, F. H., and Mettier, S. R. (1949). *Blood*, **4**, 767.
Hanafy, M. (1948). *Acta pediat. (Uppsala)*, **36**, 316.
Merskey, C., and Hansen, J. D. L. (1955). *S. Afr. med. J.*, **29**, 1078.
Rolleston, H. D., and Molony, J. B. (1912). *Proc. Roy. soc. Med.*, **5**, Part 1, Section for the Study of Diseases in Children, p. 54.
Trowell, H. C., Davies, J. N. P., and Dean, R. F. A. (1954). *Kwashiorkor*, p. 109. Arnold, London.
Wintrobe, M. W. (1951). *Clinical Hematology*, 3rd ed., p. 762. Lea and Febiger, Philadelphia.
Wright, H. P., and Bacal, H. L. (1937). *Amer. J. Dis. Child.*, **53**, 1276.

The Social Medicine Research Unit of the Medical Research Council and the General Register Office jointly carried out a statistical inquiry into deaths in infancy of children born in 1949 and 1950 in England and Wales. The main results have been published in separate papers, but the basic data are now presented in a single volume—*Social and Biological Factors in Infant Mortality*, by J. A. Heady, M.A., and M. A. Heasman, M.R.C.S., L.R.C.P., D.P.H. (H.M.S.O., £1). Detailed tables provide data on the births in 1949 and 1950 according to the age of the mother and her parity, and on the stillbirths and deaths in infancy of children born in these years according to the age and parity of the mother and the social class of the father. Other factors in analysis include the area where the parents lived, the number of previous children lost by the mother, and the duration of her marriage. Causes of death are analysed and data are also given on multiple and illegitimate births.

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VITAMINS IN BLOOD FORMATION

Megaloblastic anaemia may arise from deficiency of cyanocobalamin, as in pernicious anaemia, when absence of intrinsic factor causes defective absorption. It may also arise from deficiency of folic acid, as in the malabsorption syndrome of sprue, idiopathic steatorrhoea, and after intestinal resection, or from deficiency of ascorbic acid, as in scurvy. The interrelationships of these three vitamins in the metabolism of erythropoiesis are not exactly understood. Both cyanocobalamin and folic acid probably participate in synthesis of nucleoprotein, and ascorbic acid may function as a hydrogen donor in the conversion of folic acid to tetrahydrofolic and folinic acids.

Folic acid has long been known to induce temporary haematological improvement in pernicious anaemia, perhaps by mobilizing diminished stores of cyanocobalamin.[1] G. H. Spray and L. J. Witts[2] and R. H. Girdwood[3] found that patients with pernicious anaemia in relapse excreted smaller amounts of folic acid in the urine after a test dose than did normal subjects or patients in remission. While the extent to which folic acid is depleted has been thought to influence the clinical picture of pernicious anaemia,[4 5] it is nevertheless uncommon for supplementary folic acid to be needed in treatment.[6] E. V. Cox and colleagues[7] have recently reinvestigated this problem by testing excretion of folic acid, and found evidence of a deficiency of folic acid in 5 out of 10 patients with pernicious anaemia. The deficiency was slight and the degree of anaemia was not related to the amount of folic acid excreted after a test dose. The authors therefore concluded that deficiency of folic acid was of little importance in producing the variable clinical picture of pernicious anaemia.

After treatment with cyanocobalamin these authors noted a further temporary reduction in the excretion of test doses of folic acid and also of citrovorum factor. This could not be explained simply as a result of increased demand during regenerative erythropoiesis, since the fall was delayed until the reticulocyte peak had been passed. The reduction in excretion of folic acid after B_{12} therapy was more noticeable in severely anaemic patients, but did not appear to be related to a higher level of haemoglobin. A disorder of metabolism of the pteroylglutamate complex, rather than a quantitative deficiency, may perhaps exist in pernicious anaemia, and the correction of this disorder by B_{12} therapy may lead to a temporary increase in utilization of folic acid. The degree to which the metabolism of folic acid is impaired, rather than the extent to which it is deficient in the tissues, may perhaps influence the development of clinical anaemia.

Further evidence on the relationship between folic acid and cyanocobalamin in disease is provided by the observations of M. S. Narayanan, K. G. Shenoy, and G. B. Ramasarma.[8] They found that injection of vitamin B_{12} increased the folic acid in the serum of patients with nutritional macrocytic anaemia, while injection of folic acid in the same subjects increased the vitamin B_{12} in the serum, peak levels being reached in each case between three and seven days.

Cox and his associates[9] have also studied the metabolism of ascorbic acid in cases of cyanocobalamin deficiency. The levels of ascorbic acid in the plasma were found to be lower than in normal controls, and injected sodium ascorbate disappeared faster. After vitamin B_{12} therapy the abnormalities of ascorbic-acid metabolism were corrected in patients with pernicious anaemia, though the effect was masked in patients having a high or a grossly deficient intake of ascorbic acid. These authors thought it unlikely that depletion of ascorbic acid in the tissues influences the haematological signs of vitamin B_{12} deficiency since similar low levels were found in 7 patients with B_{12} deficiency associated with regional ileitis, and only the patient with the highest ascorbate levels in this group had a megaloblastic anaemia. The interpretation of these findings and of much earlier published data on the interrelationship of cyanocobalamin, the pteroylglutamate complex, and ascorbic acid must await a fuller understanding of the biochemical functions of these vitamins in normal and abnormal erythropoiesis.

ERGOTAMINE TREATMENT OF MIGRAINE

Various proprietary preparations of ergotamine tartrate combined with caffeine citrate and also with oestrogenic hormones have been widely advertised for the treatment of migraine. It is well to remember, however, that drug therapy alone in the treatment of this disorder is unlikely to be successful and that a careful history and thorough examination to exclude an organic basis for migrainous headaches—such as internal carotid thrombosis or anomalies of the circle of Willis—are essential before making a diagnosis of what might be termed idiopathic migraine.

When this diagnosis has been established, then efforts should be made to eradicate any precipitating factors, such as various allergies, insomnia, and refractive errors

[1] Vilter, R. W., *et al.*, *Blood*, 1950, **5**, 695.
[2] Spray, G. H., and Witts, L. J., *Clin. Sci.* 1952, **11**, 273
[3] Girdwood, R. H., *Lancet*, 1953, **2**, 53.
[4] Mollin, D. L., and Ross, G. I. M., *Brit. med. J.* 1953, **2**, 640.
[5] —— —— *Proc. roy. Soc. Med.*, 1954, **47**, 428.
[6] Unsley, C. C., in *Modern Trends in Blood Diseases*, 1955 edited by J. F. Wilkinson, p. 283. London.
[7] Cox, E. V., Meynell, M. J., Cooke, W. T., and Gaddie, R., *Clin. Sci.*, 1958, **17**, 693.
[8] Narayanan, M. S., Shenoy, K. G., and Ramasarma, G. B., *Indian J. med. Sci.*, 1957, **11**, 163.
[9] Cox, E. V., Gaddie, R., Matthews, D., Cooke, W. T., and Meynell, M. J. *Clin. Sci.*, 1958, **17**, 681.

of vision, and to see that the patient regulates his life to a steady pattern, free from severe anxieties and stress. Lack of supervision of the patient by his doctors may lead, as Dr. Raymond Greene[1] has recently pointed out in this *Journal*, to the mere writing of prescriptions for ergotamine preparations which the patient may take with increasing frequency, leading not only to more migrainous attacks but also to chronic ergot poisoning. Thus ergotamine should be used as rarely as possible and in the smallest effective dose. Because of its possible effects on the heart, the brain, and peripheral arteries it is best avoided altogether in the presence of hypertension and degenerative vascular disease. In pregnancy dihydroergotamine should be substituted, since even a very small total dosage of ergotamine may lead to severe toxic effects such as those described by E. B. French.[2] Gross sepsis, established hepatic and renal disease, anaemia, and thyrotoxicosis are also contraindications.

Acute toxic effects are characterized, soon after the drug is given, by the occurrence of nausea and vomiting. This may be controlled by giving dimenhydrinate, chlorpromazine, or prednisolone. With prolonged and frequent prophylactic ergotamine therapy there is a danger of equally prolonged vasoconstriction, which in turn may lead to thrombosis and gangrene. J. R. Graham[3] has described symptoms arising therefrom as muscle cramps, joint pains, paraesthesiae, pallor, cyanosis, thrombophlebitis, gangrene, precordial pain, abdominal pain, coronary thrombosis, and cerebral thrombosis.

It will therefore be apparent that, although this drug is of great value in aborting the prolonged and distressing symptoms of a severe attack of migraine if it is administered early in the attack, and especially if given by the subcutaneous route, its unnecessary or long-continued prophylactic use by the patient without supervision by his family doctor is fraught with danger. Migrainous subjects are common attenders at doctors' surgeries, and they should not be briefly dismissed with a prescription for one or other ergotamine preparation. An attack of migraine is often mild enough to be treated successfully by a short period of rest in bed in a darkened, quiet room and the administration of a simple analgesic—for example, codeine phosphate, perhaps together with a mild anti-emetic such as cyclizine hydrochloride. Only the severe syndrome should require the administration of ergotamine compounds. In addition, when a doctor has decided to prescribe ergotamine he should warn the patient to let him know immediately symptoms of drug sensitivity arise. For example, sudden pallor of the fingers or toes or muscle cramps should bring the patient to the doctor so that the drug can be stopped. There is a danger that the patient may feel that the occurrence of such early mild side-effects is a small price to pay for the relief of a severe and prostrating headache.

[1] Greene, R., *Brit. med. J.*, 1959, **1**, 574 and 639.
[2] French, E. B., ibid., 1959, **1**, 932.
[3] Graham, J. R., *Treatment of Migraine*, 1956. Boston.

DELIVERY BY SUCTION

The replacement of obstetrical traction forceps by an instrument employing suction was considered even before 1849, when J. Y. Simpson in Edinburgh discussed "a suction-tractor as a substitute for forceps in tedious labours".[1] Recently the work of T. Malmström, of Gothenburg, has given fresh impetus to the idea, and he has developed an improved "vacuum-extractor"[2-5] It has been the subject of enthusiastic reports in places as far apart as Sydney in Australia and Linköping in Sweden.

The instrument consists of a suction cup attached by a chain to a metal traction handle and connected to a vacuum pump and meter. The cup, which is made in four sizes from 55 to 80 mm. in diameter, is applied to the foetal scalp, and a vacuum of 0.6–0.8 kg. per sq. cm. is formed; traction is then applied intermittently in time with the uterine contractions.

W. D. Cunningham[6] has described a series of 21 cases in which he used the vacuum-extractor in preference to the conventional forceps. He was impressed by the fact that excessive or ill-directed traction was impossible because the suction cup would come away if the surface to which it was applied was not relatively flat or if the force exerted exceeded that of the suction. Moreover, the compression action of ordinary forceps was absent. O. G. A. Berggren[7] has described the results of using the vacuum-extractor in a unit at Linköping with about 1,600 deliveries a year. In a twelve-month period in 1956–7 before the vacuum-extractor was introduced the caesarean section rate was 2.1% and the forceps rate 3%. In the following twelve months the vacuum-extractor was used in 75 cases (4.6% of all deliveries), and the caesarian section rate fell to 1.3% while forceps were applied only once. The commonest indications for employing suction were foetal distress and failing uterine contractions. But, whereas Cunningham used the vacuum-extractor only when the traditional conditions for forceps extraction were fulfilled, Berggren used the instrument in eight cases before full dilatation of the cervix and in six cases while the head was still high. In this he acted in accord with Malmström's own practice, for the latter uses his instrument as Willett's forceps were once employed in inertia and in deflexion of the foetal head. Berggren is convinced that the vacuum-extractor is less hazardous to mother and baby than conventional forceps. The artificial "caput" which the suction cup caused usually faded within a day, and in only 10 of the 75 babies was the mark still apparent after a week. Further, there was no increase in the incidence of intracranial damage to the foetus after the introduction of the new instrument. Perhaps in some centres in Britain too the vacuum-extractor has been tried out, and further reports on it will be awaited with interest.

[1] Simpson, J. Y., *Monthly J. med. Sci.*, 1849, **9**, 556.
[2] Malmström, T., *Acta obstet. gynec. scand.*, 1954, **33**, suppl. 4.
[3] —— *Medicinal Markt.*, 1955, **3**, 378.
[4] —— *Jordemodern*, 1956, **69**, 427.
[5] —— *Midwives Chron.*, 1957, **70**, 184.
[6] Cunningham, W. D., *Med. J. Aust.*, 1958, **1**, 595.
[7] Berggren, O. G. A., *Svenska Läk.-Tidn.*, 1958, **55**, 3715.

Reviews

GREAT BRAINS

Grosse Nervenärzte. Volume 2. Edited by Kurt Kolle. (Pp. 251+vii; illustrated. DM. 29.40.) Stuttgart: Georg Thieme. 1959.

Neurolodzy Polsky. By Eufemiusz Herman. (Pp. 462; illustrated. No price.) Warsaw: Panstwowy Zaklad. 1958.

A History of Neurology. By Walther Riese, M.D. Foreword by Félix Martí-Ibáñez, M.D. (Pp. 223. $4.) New York: MD Publications, Inc. 1959.

It is regrettable that there does not exist in the English language a serious and full-dress account of the rise of the science of neurology with an adequate description of the personality and accomplishments of the pioneers. James Collier's FitzPatrick Lectures upon this subject, delivered at the Royal College of Physicians in 1934–5, would have supplied this need, but regrettably they were not published, and the original manuscript has never been found.

The second volume of *Grosse Nervenärzte* under the editorship of Kurt Kolle forms an excellent work of reference. It follows the lines of an earlier volume which appeared in 1946. Critical accounts of some 22 outstanding neurologists have been contributed by a team of authors belonging in the main to a younger generation. One exception is to be met with in Vogt's study of Brodmann, which is immediately followed by Hassler's account of Oscar Vogt and his distinguished wife Cécile. This is the sole instance in the book of living neurologists being under scrutiny. The subjects of biography include among others Golgi, Nissl, Alzheimer, Wernicke, von Economo, and Dubois. Three pioneers from the Paris school are incorporated — namely, Pierre Marie, Babinski, and Clovis Vincent. The only two British representatives comprise Henry Head and Victor Horsley. On the whole the biographical studies are stimulating as well as satisfying, being thoughtful contributions, well documented and critical. The lay-out resembles that of the American "Founders of Neurology," but the German volume is more informing and authoritative. In every case interesting portraits are reproduced and pilot bibliographies are appended. Kolle's work, like its earlier volume, is a "must" for every serious neurological library.

Professor Herman's account of Polish neurological achievements will surprise British readers, if only because of the impressive numbers of the exponents. Patriotically and understandably, the author has incorporated within his monograph the career of Babinski. Again, one regrets the language-barrier which inhibits the appreciation of what is obviously a fascinating story. Among the well-remembered figures we may select the record of Kasimir Orzechowski whose life was so tragically ended in 1942. Born in Przemysl in 1878, pupil of Kraft-Ebing and Obersteiner, he succeeded Flatau at the Neurological Institute of Warsaw in 1934. We value his descriptions of orgasmolepsia and of opsoclonus; and his ideas as to the correlation of von Recklinghausen's disease with tuberose sclerosis. Although Orzechowski had met Babinski only once, he always regarded him as his master in neurology and he shared many of his qualities of thought, particularly his originality.

Walther Riese's contribution is of quite a different *genre*. Although entitled a "History of Neurology," it is in reality a highly selective study of the growth of certain trends in neurological thought. In this way the traditional biographical approach is avoided. Indeed, as one turns the pages one looks in vain for mention of certain household names—for example, Gowers, Babinski, Raymond, Cajal, Foerster, Pavlov, Egas Moniz, the Vogts, and Horsley. Some others feature merely in nominal lists and without comment. Riese's pantheon holds but a small, albeit select, number of pioneers whose contributions to neurological thinking have been distinguished by dint of their profundity. Among these few we find Hughlings Jackson, von Monakow, and Lashley deservedly appraised, in a fashion indeed which contrasts with their not infrequent neglect nowadays. Among living philosophers of neurology Goldstein receives his well-merited acclaim. Riese tackles his task by devoting chapters to the development of our ideas upon nervous function; the history of the nervous impulse, of reflex action, and of cerebral localization. There is also an interesting chapter on the "rediscovery of the whole." To this valuable, if unorthodox, study of neurological history, are attached appendices which comprise a detailed bibliography; an unusual chronological table; and lists of neurological journals. Finally comes the most surprising tabulation of all, wherein specialized societies are enumerated, confused, however, with neurological institutes, neither category being comprehensively listed. The author would have been wiser to have omitted these trailers and tail-pieces.

MACDONALD CRITCHLEY.

AMINO ACIDS AND PEPTIDES

Ciba Foundation Symposium on Amino Acids and Peptides with Antimetabolic Activity. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Cecilia M. O'Connor, B.Sc. (Pp. 286+xii; illustrated. 45s.) London: J. and A. Churchill, Ltd. 1958.

This is an excellent volume which again exemplifies the high standard in organization and editing set in previous symposia by G. E. W. Wolstenholme and Cecilia M. O'Connor of the Ciba Foundation. The chairman of this symposium, Professor F. Bergel, conveniently subdivided this slice of the field of amino acids and peptides into the following headings: (*a*) chemistry, with it synthetic, structural, and physico-chemical aspects; (*b*) biochemistry, with reference to the mechanism of action and biosynthesis; (*c*) biology and experimental pathology linked to the problems of structure/activity relationships and of differences between antimicrobial and antitumour agents; and (*d*) clinical work.

Protein chemists will be interested in the authoritative accounts of disulphide cross-linking in cysteine peptides (H. N. Rydon), synthesis of cyclic polypeptides (R. Schwyzer), and the recently discovered "aminoacyl insertion" reaction (M. Brenner). The latter mechanism whereby amino acids may be inserted into a polypeptide chain through the agency of a hydroxy-amino residue is not fully understood, but many interesting points are brought out in the discussion.

Although we have to-day a number of good reviews on both general and specific antibiotics it was proper to include in this symposium a report of the current activities in this area of the Oxford school (E. P. Abraham and G. G. F. Newton), the Rockefeller school (L. C. Craig, W. Konigsberg and R. J. Hill), and of other workers (A. W. Johnson, S. Farber, J. C. Sheehan,

Exciting developments in the chemotherapy of cancer are described (H. Christine Reilly, J. M. Buchanan, J. A. Stock), and an interesting analysis of the effects of amino-acid-deficient diets on the growth of sarcoma in mice (H. E. Skipper and J. R. Thomson) presents an alternative approach to that employing tissue culture techniques. The difficulties in the interpretation of the biochemical events associated with protein and nucleic acid synthesis are apparent in the contribution on the mode of action of chloramphenicol (E. F. Gale) and in subsequent discussion throughout the symposium. The cancer problem is tough, and all will agree with the chairman that "we are still in the pre-sulphonamide days on the tumour front."

The presence of K. Balenovic (Zagreb), Natalia I. Prervodohikova and N. N. Blokhin (Moscow), and others from Italy, Sweden, Switzerland, Germany, and the U.S.A. rendered the gathering a truly international one.

This is a substantial contribution to the solution of problems connected with synthetic chemistry, fundamental biochemistry, and therapeutics.

D. P. CUTHBERTSON.

A SCHOLAR-PHYSICIAN

The Nature of Experience. The Riddell Memorial Lectures, thirtieth series delivered at King's College in the University of Durham on May 12-14, 1958. By Sir Russell Brain, Bt. (Pp. 73. 8s. 6d.) London: Oxford University Press. 1959.

It has often been said of late years that Medicine has seen the last of the scholar-physicians. Then, now and again, comes a book from the pen of a physician or surgeon to refute the saying, and to prove that the humanistic attitude still survives to illustrate and adorn the scientific outlook on the problems of man and his environment.

In these profound lectures Sir Russell Brain brings his physiological and neurological knowledge to bear on a problem of philosophy. His interest also explores perception in poetry, music, art, and the multiple aspects of human experience. He is well equipped for this self-imposed task, as his quotations from modern philosophers such as Bertrand Russell, Ryl, Ayer, and others show. He also cites Proust and Virginia Woolf in support of his arguments. He notes that the representation of experience begins at a low level biologically.

His study of hallucination is admirable. Disordered perception arising from brain lesions or psychical disturbances or drugs frequently takes the form of synaesthesia, as may occur under the influence of mescaline. *Inter alia* he advances a reasonable explanation of the vagaries of modern art which must be read to be appreciated.

John Locke, author of the famous *Essay Concerning Human Understanding*, was another Doctor of Medicine of Oxford University. His mantle has fallen on Sir Russell Brain, as these lectures demonstrate.

ARTHUR S. MACNALTY.

The proceedings of the Third World Congress of Cardiology, held in Brussels from September 14 to 21, 1958, have now been published in four volumes (Addresses, Formal Lectures, pp. 120; Abstracts of Symposia, pp. 741; Abstracts of Round Table Conferences, pp. 327; Abstracts of Communications, pp. 708). These may be obtained from Acta Cardiologica, 109, rue des deux Eglises, Brussels, 4, price 500 Belgian francs.

Correspondence

Tobacco Amblyopia

SIR,—Your annotation on tobacco amblyopia (*Journal*, June 20, p. 1528) brings to mind a case I saw in South Shields about seven years ago.

He was a fifty-year old seaman who had been taken off his ship in an American port, with loss of vision, and flown back to his home for investigation. His vision was down to 6/60 in both eyes. He presented typical signs of tobacco amblyopia. His eyes appeared healthy but he had centrocaecal scotomas, most pronounced for red. He smoked fifty cigarettes a day, all of them English brands; he neither smoked a pipe nor chewed tobacco, and drank only a moderate amount of beer. On the history I was loathe to make a diagnosis of tobacco amblyopia.

As the patient was on sick benefit, he was forced to cut down his smoking drastically. Within a few weeks he was recovering vision and when last I saw him his vision was 6/6 in both eyes.

This case convinces me that cigarette chain-smoking can produce an amblyopia.—I am, etc.,

A. T. G. EVANS.

Scotby, Carlisle.

SIR,—I was interested to read in your annotation on tobacco amblyopia (*Journal*, June 20, p. 1528) the sentence "there is no record, however, of cigarette smoking causing the disease." I am at the moment treating a male patient, aged 59 years, who suffered from tobacco amblyopia in 1950. A letter from the ophthalmologist who first saw him in 1950 states that he was smoking fifty cigarettes a day. He also goes on to say "this is the first time I have seen a case of tobacco amblyopia due to cigarette smoking."—I am, etc.,

C. B. COHEN

Manchester, 11.

Aetiology of Disseminated Sclerosis

SIR,—I was very interested in Dr. J. E. Cosnett's letter (*Journal*, June 20, p. 1588) about the incidence of disseminated sclerosis intending to study dietetic habits of South Africans, as in South Africa and I agree with him that it would be compared to those of European countries.

I have never been able to believe that the difference in temperature between South Africa and Europe explains the diminished incidence of such a disease as disseminated sclerosis. I believe disseminated sclerosis is reasonably common in Queensland, which has a high average temperature throughout the year. It is, of course, possible that an infective basis for the disease could still be responsible for the diminished incidence in South Africa. For example, a virus disease such as poliomyelitis varies enormously in its incidence in different countries.

The answer to the aetiology of disseminated sclerosis, however, remains wide open and any approach to explain the apparent rarity of the condition in South Africa would be of value. The difficulties might lie in the fact that there may be more than one factor responsible for the condition and we may still have to postulate that both an infection and a deficiency might be working together. Any work which could be done in South Africa to elucidate the cause of the infrequent cases which occur would, therefore, be of the utmost value, as it does

appear that isolated cases have occurred in native-born South Africans who have never left South Africa. These cases would, I think, repay very careful study on the line suggested by Dr. Cosnett. I consider it would also be useful if he were to investigate the incidence of retrotesbar neuritis in South Africa, which, I gather, is also extremely rare, and which is such a common early sign of disseminated sclerosis in any country.—I am, etc.,

A. M. G. CAMPBELL.

Bristol, 8.

Hand-operated Resuscitator

SIR,—I read with interest the article on a hand-operated Resuscitator by Dr. B. G. B. Lucas and his colleagues, (*Journal*, May 2, p. 1165). There is no doubt that there is a very real need for such an apparatus both for the reasons mentioned in the article and for industrial emergencies such as cases of electrocution and cyanide poisoning.

I feel however that it is a pity that the facepiece, in every other way so well designed, could not have been made with a straight-forward British Standard push-on attachment as in the case of an anesthetic facepiece, in view of the fact that, like the Champetier de Ribes's bag, it is a rarely used piece of emergency equipment, and that the one time it is badly needed the facepiece will have perished and no readily available substitute will be to hand. This modification would also facilitate convertion to endotracheal intubation with manual control should the need arise.—I am, etc.,

C. D. SANDERS.

British Military Hospital,
Singapore.

Diabetes in the Tropics

SIR,—Your recent leading article on diabetes in the tropics (*Journal*, January 24, p. 219) and Dr. J. E. Cosnett's paper on the Natal Indian diabetics (p. 187) prompt us to record some of the developments in the treatment of diabetes at the King Edward Hospital, Durban, since Dr. Cosnett wrote his paper 18 months ago. During 1958 expansions in the hospital allowed the establishment of a diabetic clinic for Zulu and Indian patients. Out of a total of over 650 patients at present attending we have extracted information on the first 405 (105 Zulus, 300 Indians).

The chief problem with impecunious diabetics is that of trying to diet them satisfactorily. On account of poverty their diet is very high in carbohydrate. We devoted our most earnest efforts to impressing upon our patients the need to restrict carbohydrate. All patients are lectured to in Zulu and English about dieting, urine testing, and syringe technique, and they are each given a rough diet sheet in keeping with the customs of both races. In a clinic in which no less that five types of diabetics are seen we have for obvious reasons avoided the use of the terms "Type 1" and "Type 2." Table I shows the terms that we have used in our clinic. It is interesting to note that, unlike Hugh-Jones in Jamaica,[1] we find the "J" type of diabetic only in patients of Indian extraction and not in the African. In Dr. Cosnett's paper he quoted that 8% of all his Indian patients were of the "J" type. In the present series, we have found only 2%. The reason for this is twofold: firstly, we have a number of thin young Indian diabetics, who have been satisfactorily controlled on the oral antidiabetic drugs, and in whom we have never established insulin requirements because of the facility with which they have been controlled on oral therapy. Secondly, because we have applied most stringently our criteria (see Table I) in the diagnosis of the "J" type—any patient who has shown acetone on even one occasion being excluded from this category.

In Table II we have set out the methods of treatment that have been employed in our first 405 cases—the criterion of control being that which would be regarded as "fair" in clinics in the U.S.A. or the U.K.

TABLE II

Method of Treatment	Indians (300)			Zulus (105)		
	Male	Female	Total	Male	Female	Total
Diet only	15	31	46	2	5	7
Diet and 0–40 units insulin daily	17	17	34	13	15	28
Diet and over 40 units insulin daily	9	19	28	8	14	22
Diet and oral antidiabetic drug	58	134	192	15	33	48
Totals	99	201	300	38	67	105
Successfully "converted" from insulin to oral antidiabetic drug	25	40	65	12	15	27

Dr. Cosnett noted in this paper that 11 out of a total of 207 patients were controlled on tolbutamide. Table II shows how much this has changed. Because of primitive syringe hygiene we have tried to wean as many patients as possible off insulin, and in our first 405 patients we have converted 92 from insulin to tolbutamide or another antidiabetic drug. These preparations have proved admirable in many patients, including many young people, of both races. Table II shows that many of our fat middle-aged diabetics are on the oral antidiabetic preparations (principally tolbutamide). We realize fully that this is bad diabetic practice, but, as the incomes of so many of our patients prevent their being able to afford other than a diet rich in carbohydrate, our aims have been to try to relieve the troublesome symptoms of diabetes and to render the urine as free of sugar as possible. In this respect the oral antidiabetic drugs (tolbutamide, chlorpropamide, and metahexamide) have

TABLE I

Name in Our Clinic	Equivalent	Indians (300)			Zulus (105)		
		Male	Female	Total	Male	Female	Total
"Senile"	Generally over 60 yr. at onset; often underweight; generally easy to control on oral drug, or small dose of insulin	22	24	46	2	9	11
"Fat middle-aged"	Middle-aged insulin-resistant patients; "Type 2"	66	140	204	24	33	57
"J" type ..	Under 40 yr. at onset, always thin, insulin-resistant (80 or more units daily); not liable to ketosis if insulin is withdrawn	—	5	5	—	—	—
"Non-J" juveniles	Young, labile, fat, insulin-sensitive patients; often fat; in Zulus, easily ketotic — Fat	2	19	44	7	17	37
	Thin	10 → 12	13 → 32		4 → 11	9 → 26	
Chronic pancreatitis patients	Diabetes due to chronic pancreatitis	1	—	1	—	—	—

proved invaluable. In only four instances out of the 92 "conversions" from insulin to oral therapy had the patient to be put back on to insulin again. These conversions included not only fat middle-aged diabetics (who should not really have been put on to insulin prior to their being referred to the clinic), but also several patients who had been ketotic; one Zulu woman, who had been admitted in diabetic coma, has now been satisfactorily controlled for over six months following an initial period on insulin. Hopes that the use of oral preparations would reduce the insulin requirements of the "J" type diabetics have not been realized, though, as stated above, certain of the milder thin young diabetics have been well controlled by these drugs; but we are not really in a position, yet, to say whether these are in fact "J" types or not.

Diabetes is reputedly rare in the African. In a recently published monograph on sickness in the African[2] a series of 17 is reported to have been collected in two years; of these 14 were males, and most were between 20 and 40 years of age; treatment was regarded as being very unsatisfactory. In eight months we have been able to collect 135 Zulu diabetics (annual hospital turnover: 600,000 out-patients). Their study has proved most interesting and a detailed paper upon them is in the process of preparation.

We find there is a marked similarity between the European and Zulu diabetics; the Indians differ from both. in that they generally have a much milder form of disease, are more resistant to insulin, and it is in them only that the "J" type of diabetic is found in Natal.

So far, we have counted ourselves successful in two ways: firstly in the regularity with which our patients attend, and secondly in that we have achieved weight losses in our Indian patients, which we would formerly have considered impossible; it is true to say that rigorous dietary control would reduce the number of patients in our clinic to one-third. We hope that, by trying to discipline our Indian patients, we may in time be able to avert the terrible diabetic complications seen in them, which have been summarized by Dr. Cosnett. On the whole our Zulu patients have been good and co-operative in their control, and they are infinitely more tractable patients than the Indians.—We are, etc.,

G. D. CAMPBELL.
W. G. MCNEILL.

King Edward Hospital,
Durban, S. Africa.

REFERENCES

[1] Hugh-Jones, P., *Lancet*, 1955, 2, 891.
[2] Gelfand, M., *The Sick African*, 1957. Juta and Co., Capetown.

Boxing

SIR,—Boxing in the only game in which you try to injure your opponent. Since the *coup de grace* is the "knock-out" it is what every boxer aims at; no matter how much he has been out-pointed in previous rounds, he is the winner if he scores a knock-out. For once I would agree with Dr. Edith Summerskill about the dangers to the brain.

Another termination of a fight is when one boxer sustains a cut-brow, which by reason of the bleeding blinds him. He is the loser. What seems un-British is that his opponent is instructed to play to it. A stout, silk-mattress suture inserted during the interval would meet the case. The cut could be stitched subcutaneously at the end of the fight.—I am, etc.,

A. P. BIRTWISTLE.

London, S.W.16.

SIR,—I suggest that Dr. J. A. Waycott (*Journal*, June 20, p. 1591) reads the reply[1] from the honorary medical officers of the Amateur Boxing Association to the leading article in the *Lancet*[2]. Of course there can be no "official policy" of the B.M.A. on boxing, or for that matter on ski-ing, Rugby and Association football, motor racing, motor-cycle racing, hunting, or horse-riding, at which, on percentage, there is a greater number of fatalities and injuries.

No one is obliged to box and the medical control of boxers is as high as, if not higher than, that of any sport May I repeat the Prime Minister's statement in the House of Commons on the subject on June 18: "I am not persuaded that the appointment of a Select Committee would be appropriate . . . . I think we should look to the bodies responsible for controlling the sport, both amateur and professional, to pay due regard to all these matters".[3]—I am, etc.,

J. L. BLONSTEIN.

London, W.1.

REFERENCES

[1] *Lancet*, 1959, 1, 1280.
[2] ibid, 1959, 1, 1185.
[3] *Hansard*, 1959, 607, No. 128, Col. 647.
London, S.E.18.

Printing the "B.M.J."

SIR,—I wish to protest most strongly against the publication of the *B.M.J.* by non-union labour during a dispute. At a time when you are supporting a doctors' wage claim it is unwise as well as immoral to take steps which militate against successful action by a section of the public.

It is nonsense to suppose that any doctor requires the *B.M.J.* in any given week to carry on his day-to-day practice. As for the accusation of "sabotage of the N.H.S.", I find this hypocritical in one who recently advocated a walk-out from the N.H.S., and who looks with favour on schemes of the Fellowship for Freedom—I am, etc.,

G. RICHMAN.

B.C.G. Vaccination

SIR,—It is disappointing to note that the combined American authors in their paper, "The Case against B.C.G." (*Journal*, June 6, p. 1423), take no cognizance of the fact that B.C.G. vaccination is at least a complete prevention against the two very common forms of childhood tuberculosis—tuberculous meningitis and miliary tuberculosis. It is also highly probable that it will prevent metastatic foci developing in the genito-urinary system. This is of great importance in adolescent girls where a primary infection may well result in life-long sterility. A further factor that they do not stress is that in B.C.G. vaccination at least the site of election of the primary is extra thoracic. This will at least ensure that pulmonary endogenous breakdown, with spreading disease in the lungs, does not occur. It may be argued by many that this is of minor importance as the majority of re-infection tubercle is of exogenous nature, but so far this has never been satisfactorily proved.

I think that there are many doctors who would hardly agree with our American colleagues that naturally occurring tuberculous lesions are "benign."

We are all dependent on each other, and with the rapid increase in air travel the world is a very much smaller place than it was. It is quite unrealistic to pre-

tend that by the application of hygienic and therapeutic measures a country can be rendered permanently free of tuberculosis. No country can establish a permanent *cordon sanitaire*. I certainly agree with the authors that the widespread use of B.C.G. will interfere with the epidemiological investigation of tuberculosis epidemics and also the evaluation of therapeutic and preventive measures against the disease. This would appear to me to be a small price to pay in relation to the obvious benefits conferred by vaccination.—I am, etc.,

P. O. LEGGAT.

Obituary

G. M. FYFE, C.B.E., M.B., F.R.C.P.Ed., D.P.H.

Dr. G. M. Fyfe, for many years medical officer of health for the County of Fife, died at his home at Cupar on June 2, after a long and trying illness borne with great fortitude

George Matthew Fyfe was born at Aberdeen on May 10, 1895. Educated at Robert Gordon's College and at Aberdeen University, he took an honours degree in classics before the first world war and graduated in medicine in 1920. He was captain of the university rugby fifteen and won a trial cap for Scotland. During the first year of the war he served with the university battalion of the Gordon Highlanders, receiving an eye wound, and from 1915 to 1918 he assisted in the pathological laboratory of the 1st Scottish General Hospital. After graduation he was appointed Carnegie research assistant in the physiology department of Aberdeen University and assistant medical officer of the general medical and cardiac clinic at the Ministry of Pensions, Aberdeen. In 1923 he was appointed assistant medical officer of health for Aberdeen, and two years later he took the D.P.H. He moved to Fife in 1926 as medical officer for St. Andrews and as bacteriologist of the James Mackenzie Institute for Clinical Research. Becoming deputy medical officer eight years later.

W.B.P. writes: Both national and international recognition came the way of Dr. George Matthew Fife. In 1943 he was appointed a member of the advisory committee set up by the Secretary of state for Scotland to advise on the medical aspects of problems relating to the health of the people. Among numerous other important appointments he was a member of the Scottish Health Services Council and of the several boards of management of the Fife hospitals. On two occasions he was the British delegate at study courses held by the World Health Organization, and in 1957 he went to West Africa, under arrangements made by the Colonial Office, to serve as an expert advisor on public health matters. In 1950 he was elected a Member of the Royal College of Physicians of Edinburgh, being admitted a Fellow in 1953. He was appointed C.B.E. in 1956.

Fyfe had a tremendous urge for work and the gift of getting the very best out of his staff, who had a deep respect and admiration for him. He brought to his post as county medical officer a prestige and dignity in keeping with the highest traditions of his calling, and the members of his health and welfare committee had absolute confidence in him. To his colleagues in the profession he was a strong and forceful personality who spoke his mind with conviction in debate, but who could also be the essence of kindness and helpfulness when his counsel was asked for in professional matters. He was president of the Fife Branch of the B.M.A. in 1936-7. For recreation he played golf—he was a member of the Royal and Ancient Golf Club — and shooting and angling also appealed to him greatly; he always looked forward to his annual holiday in the north. He leaves a widow and three sons, to whom our deep sympathy is extended.

D. B. EVANS, M.R.C.S., L.R.C.P.

Dr. D. B. Evans, a well-known general practitioner in N. Wales, died suddenly at Wrexham on June 18, aged 72.

David Benjamin Evans was born at Llanybyther, Carmarthenshire, on March 5, 1887, and was educated at Llandyssul Grammar School, at the University of Wales, and at St. Bartholomew's Hospital, qualifying in 1912. After holding the posts of resident medical officer at the City Road Chest Hospital, London, and the Papworth Tuberculosis Colony, he became successively medical superintendent of the North Wales Sanatorium, Llangwyfan, Denbighshire, the South Wales Sanatorium, Talgarth, Breconshire, and the Standish House Sanatorium, Gloucester. In 1923 he entered general practice in the Coedpoeth district of Wrexham, and later became a member of the honorary staff of the local hospital.

Dr. A. WESLEY HILL writes: The many friends of David Benjamin Evans feel a deep sense of loss at his passing. Only two years ago we presented "D.B." with an illuminated address as a token of our appreciation of the valuable services he had rendered the medical profession over many years. Endowed with great energy and ability, he conducted a successful medical practice at Coedpoeth, near Wrexham, and yet devoted considerable time to medico-political affairs, in which his aptitude gave him an outstanding position of leadership. In 1923 he was elected a member of the Denbighshire panel committee, and he was secretary of this committee from 1928 till 1948. With the inception of the National Health Service he was elected to the executive council for Denbigh and Flint and to the secretaryship of the local medical committee for this area. He held this latter position until 1954, and during this continuous period of 26 years he carried out these secretarial duties with great efficiency. His colleagues could always rely on his ready help and wise counsel.

He served the medical profession not only locally but in a wider sphere. He was one of the two elected representatives from Wales on the Central Insurance Acts Committee from 1940 to 1948 and subsequently in the same capacity he served on the General Medical Services Committee during the important period when National Health Service was coming into being. In 1948 also he was appointed by the Minister of Health to the Medical Practices Committee and he served on this until 1955. His services and loyalty to the British Medical Association, both in the local Division of which he became a chairman, and in the North Wales Branch, of which he was president, culminated in his being elected to serve on the B.M.A. Council in 1950.

Alongside these medico-political concerns, "D.B." had an interest in local government affairs and was at times a member of parish and rural district councils. He was also a high ranking Freemason. But most of all, and even with these many and varied interests, "D.B." was a good doctor, beloved and popular among his patients. A busy man with a tremendous interest in life has now entered into his rest. We tender sympathy to his widow, Mrs. Evans, and to his son, Dr. Elgin Evans.

Medical News

Sheffield University.—At a meeting of the Council on July 3, Dr. S. R. ELSDEN, PH.D., was appointed to the newly created chair of microbiology as from October 1. He is at present senior lecturer in charge of the department of microbiology. The following appointments were also made to the university staff: Dr. R. S. DUFF (senior lectureship in medicine), Dr. I. E. GILLESPIE (lectureship in surgery), Dr. D. N. WARRELL (lectureship in obstetrics and gynaecology), Dr. L. GRIMSHAW (lectureship in psychiatry).

Medical Insurance Agency.—At the Agency's thirty-first annual general meeting, it was agreed that the 21 years of service of the general manager, Mr. A. N. DIXON, should be commemorated by two foundation scholarships at the Royal Medical Foundation of Epsom College. They will bear his name, and be endowed by a seven-year covenant of £1,000 a year. The chairman, Dr. J. I. FENTON, said that 1958 had had been a highly successful year, and that the sums assured in completed life and endowment contracts amounted to £7,713,000.

Society of Apothecaries, London.—On June 30 the Society's 1959 Gold Medal in therapeutics was presented to Professor A. BRADFORD HILL, F.R.S., in recognition of his work in the field of medical statistics.

Institute of Psychiatry.—The Institute of Psychiatry in the University of London has received a gift of £184,000 from the Isaac Wolfson Foundation. It will be used for a new building containing lecture theatres, common rooms, and other amenities for students and staff at the Maudsley Hospital, Denmark Hill.

Liverpool University.—Dr. T. C. GRAY has been appointed professor of anaesthesia from October 1. Dr. E. SHERWOOD JONES is to be senior lecturer in the Department of Medicine, from the same date.

Royal Society of Tropical Medicine and Hygiene.—The Society's annual general meeting was held on June 18, when Sir WILLIAM MACARTHUR was inducted as president for the next two years. Colonel H. E. SHORTT, F.R.S., was presented with the Society's Manson Medal, and Dr. J. R. AUDY with its Chalmers Medal. Afterwards Professor W. ST. C. SYMMERS illustrated with lantern slides a talk on "Clinico-pathological Observation on some cases of Fungal Infections and other Tropical Infections met with in Britain." His commentary illustrated the clinical detective work that is necessary to trace to their source the odd cases of exotic infection that crop up from time to time in this country.

Royal College of Surgeons, England.—On July 2, Mr. R. V. COOKE (Bristol Royal Hospital) who polled 718 votes, and Mr. H. OSMOND-CLARKE (The London Hospital) who polled 675, were elected members of the College council. Runners-up were Mr. N. R. BARRETT (St. Thomas's Hospital) with 550 votes, and Mr. E. G. MUIR (King's College Hospital) with 534. In all, 2,455 Fellows voted, and in addition 40 votes were found to be invalid. On June 24 Lord KINDERSLEY was elected to an honorary fellowship.

COMING EVENT

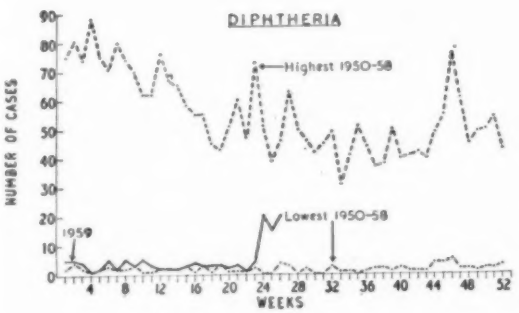
Fourth European Congress of Allergy.—Bedford College, Regent's Park, London, N.W.1., September 1-4. Details: Dr. A. W. FRANKLAND, Wright-Fleming Institute of Microbiology, St. Mary's Hospital, London, W.2.

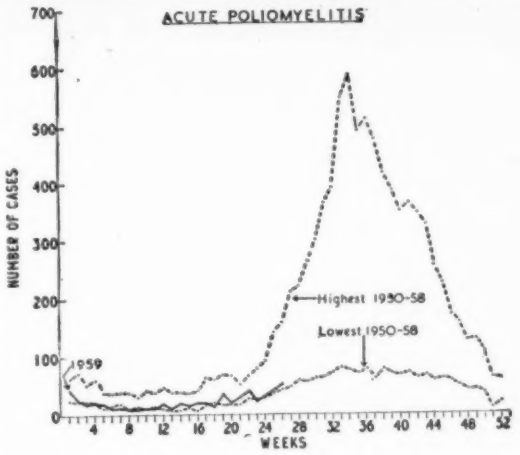
European Association against Poliomyelitis.—Munich, September 6-9. Details: Secretary of U.K. Committee for Poliomyelitis, c/o Royal College of Physicians, 12, Pall Mall East, London, S.W.1.

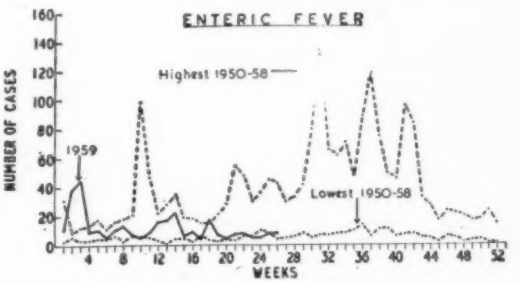
European Society of Haematology.—7th Congress, London, September 7-12. Details: Secretary, Department of Pathology, St. Mary's Hospital, London, W.2.

International Union against Venereal Diseases and Treponematoses.— General Assembly, County Hall, Westminster, October 13-16. Details: Dr. C. S. NICOL, Lydia Department, St. Thomas's Hospital, London, S.E.1.

Vital Statistics







ANY QUESTIONS?

Verruca from Bare-foot Dancing

Q.—*Could the occurrence of verruca in schoolgirls be caused by dancing in bare feet on wooden floors?*

A.—This is certainly a view taken by many dermatologists, though chiefly by inference rather than direct and conclusive evidence. It is known that warts may be inoculated into scratches and minor injuries of that kind, but it is not known whether this is the only means by which they are transferred by one person to another. There can be no doubt that bare-foot dancing on wooden floors leads to minor injuries of this sort. It also seems likely that walking bare foot in changing rooms, swimming pools, and the like is a means of spreading the infection. An impression is that plantar warts are more common in girls than in boys. If plantar warts are occurring in a girls' school the cessation of bare-foot dancing or gymnastics, except perhaps on a grassy field, is advisable.

Ferning of Mucus

Q.—*What is meant by "ferning" of the cervical mucus?*

A.—If cervical mucus, obtained in the middle weeks of the menstrual cycle (6th–22nd days), is spread on a glass slide and allowed to dry, it shows a phenomenon called variously "crystallization," "arborization" or, because it resembles the fronds of a fern, "ferning." Ferning is not seen in the cervical mucus of the first week of the cycle, nor in the cervical mucus of castrate or post-menopausal women except after the administration of oestrogen. A positive fern-test, therefore, is said to afford evidence of

oestrogen activity, and a negative test to indicate the absence of oestrogen or the presence of a fern-inhibiting substance such as progesterone. If ferning is seen at mid-cycle but disappears in the premenstrual phase (after the 22nd day), it is presumed that the change is due to progesterone effect and is therefore presumptive of ovulation. Indeed, the power of progesterone to inhibit ferning has been employed recently as a means of assessing the progestational activity of new steroid preparations. If the fern-test remains positive until the start of a menstrual period it is said to indicate that that cycle was anovular.

The mucus may be obtained from the cervix by an applicator or a "spoon" or a pipette. Slides and instruments for the test must be washed and sterilized in distilled water, since electrolytes in tap water may give a false positive test; the presence of blood in the sample of mucus may produce a false negative test.

The mechanism of fern formation is not specific for cervical mucus but is found at all times in nasal mucus, saliva, and solutions containing electrolytes and mucin.

REFERENCES

Greenblatt, R. B., *Amer. J. Obstet. Gynec.*, 1958, **76**, 626.
Roland, M., ibid., 1952, **63**, 81.
Zondek, B., and Rozin, S., *Obstet. and Gynec.*, 1954, **3**, 463.

T.A.B. Vaccine and Rheumatoid Arthritis

Q.—*Might a course of intravenous T.A.B. vaccine and blood transfusion be helpful in a case of rheumatoid arthritis which has failed to respond to a combination of aspirin and corticosteroids?*

A.—Rheumatoid arthritis is a very variable disease and remissions have occurred during the course of treatment on many different regimes. If the patient is severely anaemic this might be due to faecal blood loss, since both corticosteroids and aspirin occasionally cause this. Stopping aspirin or corticosteroid and changing over to A.C.T.H., phenylbutazone, etc., may improve the anaemia or, if the anaemia is of the dyshaemopoietic variety associated with inflammatory processes, it may not. Transfusion has no value apart from temporary improvement of the anaemia. Intravenous T.A.B. vaccine is sometimes followed by a transient improvement but is unlikely to be of great help in the long run.

Risk of Biopsy

Q.—*Does taking material for biopsy from a growth in the breast or bowel increase the risk of metastases should it prove to be malignant?*

A.—There is no evidence that taking material for biopsy from a malignant growth in the breast or bowel increases the risk of metastases. The biopsy should be done with the least trauma to the tumour. In the case of a doubtful circumscribed lump in the breast it is probably better to excise it cleanly rather than to cut a piece out, and when there are facilities for immediate histological examination by the frozen section technique the diagnosis can be made immediately and a radical mastectomy carried out without any delay.

Cholesteatoma

Q.—*What is the aetiology and treatment of a cholesteatoma?*

A.—Cholesteatoma occurs in the middle-ear cleft, sometimes in association with chronic suppurative otitis media. There are two types. The primary cholesteatoma, or epidermoid tumour, is seen most often in the temporal bone and usually quite independent of the middle ear itself. It may also be found in other parts of the skull, including the sphenoid and the orbit. It is thought to be of embryonic origin. In the temporal bone it tends to attack the internal ear and may cause facial palsy and loss of hearing and vestibular function.

The much commoner secondary cholesteatoma is found in the upper part of the middle-ear cleft in association with chronic infection. The most favoured theory of its origin is that squamous epithelium grows in through a perforation in the upper part of the tympanic membrane from the skin of the outer ear and there it forms into a characteristic mass of cholesteatoma.

Cholesteatoma is in the habit of destroying bone, it is thought by pressure, and may allow infection to enter the inner ear or the intracranial space. This may lead to serious complications, and for this reason every case of cholesteatoma calls for complete eradication by surgical means, very often a radical mastoid operation is needed.

Antimalarial Drugs

Q.—*(1) Is pyrimethamine taken prophylactically harmful to children, or to the foetus in pregnant women? (2) Is it reasonable to use chloroquine as a suppressant and therapeutic agent in the same patient?*

A.—(1) Pyrimethamine in prophylactic dosage is to all intents non-toxic. (2) Shloroquine is an efficient drug for both purposes; there is no evidence of the development of drug-fastness by any known strain of parasite.

Chemotherapy and Ectopic Pregnancy

Q.—*Is there any evidence that ectopic pregnancy is on the increase as a result of chemotherapy and antibiotic therapy?*

A.—The point is still uncertain. There have been recent papers purporting to show a relationship between the use of chemotherapy and antibiotics and an increased incidence of ectopic pregnancy[1–3] The reason given is that such treatment of pelvic infection more often prevents complete closure of both tubes; there is, therefore, more often partial tubal obstruction, such as partial agglutination of mucosal folds, and this, together with consequent altered physiology, favours hold-up of the fertilized ovum in the tube. Others have failed to confirm this,[4–6] but certainly whenever conception occurs in a woman treated for genital tuberculosis, ectopic pregnancy must be thought of and excluded.[6]

REFERENCES

1 Johnson, W. O., *Amer. J. Obstet. Gynec.*, 1952, **64**, 1102.
2 Krohn, L., Privet, M. S., and Gotlib, M. H., *J. Amer. med. Ass.*, 1952, **150**, 1291.
3 Johnson, C. G., and Post, L. I., *Surg. Gynec. Obstet.*, 1954, **98**, 481.
4 Fontanilla, J., and Anderson, G. W., *Amer. J. Obstet. Gynec.*, 1955, **70**, 312.
5 Donovan, W. H., *Obstet. and Gynec.*, 1956, **7**, 694.
6 Halbrecht, I., ibid., 1957, **10**, 73.

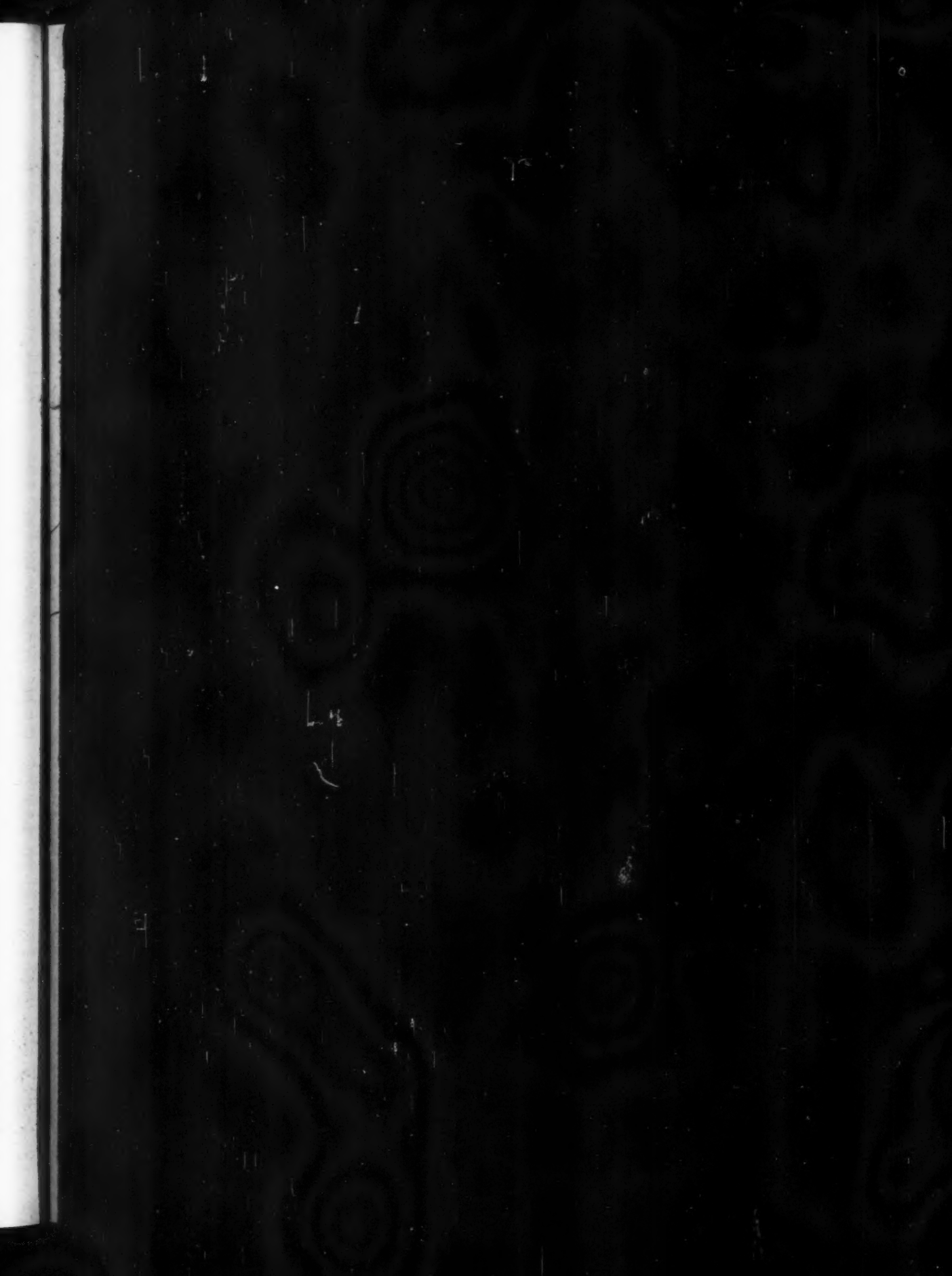
Benzpyrene in Toast

Q.—*Does toast contain benzpyrene? Is it carcinogenic?*

A.—Burnt toast and other foods do contain minute amounts of benzpyrene, but the amounts are considered to be negligible as a carcinogenic hazard, since they are not more than would be consumed in untoasted bread exposed to the atmosphere of a large town.

Promethazine in Urticaria

Q.—*Is there any harm in continuing indefinitely treatment with promethazine 25 mg. every night in a case of urticaria in which all other treatments have failed?*

A.—There is very little risk in continuing promethazine indefinitely in such a case.

A Short History of the Order of St. John, by E. D. Renwick, gives an interesting account of this Order and of the humanitarian work for which it has been famous for many centuries. This well-illustrated booklet has been written primarily for cadets joining the Brigade, but will appeal also to others interested in its history and achievements. A useful addition to future editions would be a select bibliography of previous publications on the subject. The booklet has been published by the Order at St. John's Gate, Clerkenwell, London, E.C.1 (pp. 83; illustrated; 2s. 6d.).